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## EXPLORATION AND DEVELOPMENT OF BENZIMIDAZOLE-BASED PHOSPHINE LIGANDS TOWARDS SUZUKI-MIYAURA CROSS-COUPLING

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M.Phil

The Hong Kong Polytechnic University 2010

### The Hong Kong Polytechnic University Department of Applied Biology and Chemical Technology

### Exploration And Development Of Benzimidazole-Based Phosphine Ligands Towards Suzuki-Miyaura Cross-Coupling

Yeung Chung Chiu

A thesis submitted

in partial fulfillment of the requirements

for the degree of Master of Philosophy

(JULY 2010)

#### **Certificate of originality**

I hereby declare that this thesis is my own research work carried out since my registration at the Hong Kong Polytechnic University for the degree of Master of Philosophy in September, 2008, and that, to the best of my knowledge and belief, it reproduces no material previously published or neither written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

YEUNG CHUNG CHIU July, 2010

#### Abstract

"Exploration and development of benzimidazole-based phosphine ligands towards Suzuki-Miyaura cross-coupling"

Submitted by YEUNG CHUNG CHIU

For the degree of Master of Philosophy

At The Hong Kong Polytechnic University in August, 2010

The research study is focused on the development of easily accessible heterocyclic phosphine ligands. The first part of the investigation is the attempted study of electronic effects towards the reactivity of indolyl phosphine ligands while the second part is the design and synthesis of newly developed benzimidazole-based phosphine ligands and their applications on Suzuki-Miyaura Coupling.

In the study of indolyl phosphine ligand, we tried to examine the electronic effect by the incorporation of different substituted groups on the 5-position of the indole ring on the ligand template. We aim to study the importance of the electronic density on the phosphorus atom over the reactivity of the ligands. We propose that the reactivity of the ligands should be directly proportional to the electron density of P donor atom of ligands. A family of 5-substituted indolyl phosphine ligands were successfully prepared and their reactivity was compared by the same Suzuki coupling reaction under mild reaction conditions in order to demonstrate their reactivity differences. We believe this research findings will contribute to the future development of related ligands.

In my second project, a new scaffold, benzimidazole, was used for the ligand design. Benzimidazole is attractive as it is commercially available with a reasonable price. In addition, the synthesis of benzimidazole-based phosphine ligand is atom economic that less side products are formed. However, using ligands with benzimidazole scaffold is not electron-rich enough for Suzuki coupling. Based on the research concept of my first project, we modified the ligand design by adding two methyl groups on the benzimidazole scaffold. The new dimethyl benzimidazole-based phosphine ligand is highly effective for Suzuki coupling of both activated and deactivated aryl chlorides with moderate catalytst loading.

#### **Publications**

1. So, C. M.; <u>Yeung, C. C.</u>; Lau, C. P.; Kwong, F. Y. J. Org. Chem. 2008, 73,

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#### Abbreviation

Ac	acetyl
Ad	adamantyl
Ar	aryl
Bn	benzyl
Bu or <i>n</i> Bu	(primary) butyl
Bz	benzoyl
COD	1,5-cyclooctadiene
Ср	cyclopentadienyl
Су	cyclohexyl
DCE	1,2-dichloroethane
DCM	dichloromethane
Dppe	1,1'-bis-(diphenylphosphino)ethane
Dppp	1,1'-bis-(diphenylphosphino)propane
Dppb	1,1'-bis-(diphenylphosphino)butane
Dppf	1,1'-bis-(diphenylphosphino)ferrocene
DMF	dimethyl formamide
E+	electrophile
eq.	equivalent
Fur	furyl
GC	gas chromatography
h	hour
HPLC	high-performance liquid chromatography
HPMS	high-resolution mass spectrometry
<i>i</i> Bu	isobutyl
iPr	isopropyl
J	coupling constant (in Hertz)
LDA	lithium diisopropylamide
[M]+	transition-metal pre-catalyst
Me	methyl
min	minute
MS	mass spectrometry
Ms	mesyl, methanesulfonyl
m/z	mass-to-charge ratio (in mass spectrometry)
Naph	naphthyl
NBD	norbornadiene
NMR	nuclear magnetic resonance

nucleophile
phenyl
propyl
polystyrene-diethylsilyl
polystyrene-ethyl
phase transfer catalyst
pyridine
room temperature
secondary butyl
tertiary butyl
tetrahydrofuran
toluene
tosyl, toluenesulfonyl
xylene
special optical rotation
Hammett substituent constant
normalized Et(30) solvent polarity

#### **Chapter 1**

#### Introduction

#### **1.1 Suzuki coupling reaction**

The last several decades have seen growing attention placed on the synthesis of compounds containing heterobiaryl moieties, which are commonly found in polymers,<sup>1</sup> ligands,<sup>2</sup> pharmaceuticals,<sup>3</sup> and functional materials.<sup>4</sup> Among the reported synthetic pathways, the palladium catalyzed Suzuki–Miyaura cross-coupling reaction between heteroaryl halides and arylboronic acids provides a general and applicable method for the preparation of heterobiaryl compound.<sup>5</sup> The Suzuki reaction, discovered by Akira Suzuki in 1979,<sup>6</sup> of aryl and vinyl halides or triflates with boronic acids has drawn a great attention because of its commercial availability of boronic acids.<sup>7</sup> They are nontoxic and stable to heat, air and moisture. And less side products are formed after the catalysis. The desired products are easily purified by column chromatography.



(Scheme 1: General equation for Suzuki coupling)

Among the aryl halides, aryl chlorides are the most preferable substrates because of their low cost and the wide diversity of available compounds.<sup>8</sup> However, a major limitation is that the bond dissociation energies for C-Cl bond is the second highest

among the other carbon-halide bond, resulting in poor reactivity of aryl chlorides.<sup>9</sup>

#### 1.1.1. Suzuki coupling mechanism

The proposed mechanism of the Suzuki reaction is a three-step process. (Figure 1)



(Figure 1: The mechanism of the Suzuki reaction)

The first step is the oxidative addition in which the aryl halide is added to the palladium (0) metal and Pd is oxidized into Pd<sup>2+</sup>.Secondly, during transmetallation,<sup>10</sup> the organic group attached to the boron atom become a more potent nucleophile by reacting with hydroxide ion from base, followed by a substitution reaction. The role of base is to facilitate the slow transmetallation of the boronic acid by forming a more reactive boronate species that can interact with the Pd metal center. The organic group attached to boron is transferred to the Pd<sup>2+</sup> ion and replaces the halide ion. Finally, the complex undergoes reductive elimination to produce the desired bi-aryl product and regenerate the original palladium (0) catalyst.

#### 1.2. Metal for Suzuki coupling

#### 1.2.1. Nickel-catalyzed Suzuki coupling

In 2006, Fu reported the use of amino alcohols as ligands for Nickel-Catalyzed Suzuki reaction of unactivated alkyl halides with aryl boronic acids.<sup>11</sup> The alkyl halides included secondary bromides, secondary iodides and primary iodides. The general equations are shown as follow:

$$\begin{array}{c} 6\% \text{ Nil}_{2} \\ \hline R_{alkyl} - X + (HO)_{2}B - R & \underbrace{6\% \text{ trans-2-aminocyclohexanol}}_{NaHMDS (2 \text{ equiv})} \\ X = Br, I & 1.2 \text{ equiv} & i-propanol, 60^{\circ}C \end{array} \xrightarrow{R_{alkyl}} R_{alkyl} - R$$

(Scheme 2: Nickel-catalyzed Suzuki coupling of aryl bromide and aryl iodide)

 $\begin{array}{c} \begin{array}{c} & 6\% \text{ Nil}_2 \text{ glyme} \\ 12\% \text{ prolinol} \\ \hline \\ \text{KHMDS (2 equiv)} \\ 1.5 \text{ equiv} \end{array} \xrightarrow{} \begin{array}{c} \text{R}_{alkyl} - \text{R} \\ \hline \\ \text{KHMDS (2 equiv)} \\ \text{i-propanol, } 60^{\circ}\text{C} \end{array}$ 

(Scheme 3: Nickel-catalyzed Suzuki coupling of aryl chloride)

The nickel-catalyzed reaction offered a few advantages that after the catalysis, the desired product was easily separated from the catalyst mixture. In addition, the nickel complex is air stable, less costly and easy to prepare for catalyst. The above properties are important when considering the scale-up of the reaction.<sup>12</sup>

Apart from Fu, Miura has also reported the nickel-catalyzed Suzuki-Miyaura cross-coupling for the first arylation of 3-chloro-2-methoxycarbonly benzo[b]thiophene in 2009 (Scheme 4).<sup>13</sup>

$$\begin{array}{c} CI \\ \hline \\ S \end{array} COOMe + Ar-B(OH)_2 \end{array} \xrightarrow{\begin{array}{c} 5 \text{ mol\% NiCl}_2(dppe) \\ 2.0 \text{ equiv. } K_3PO_4 \\ \hline \\ toluene, 120^\circ C, 6h \end{array}} \xrightarrow{\begin{array}{c} Ar \\ \hline \\ S \end{array} COOMe$$

(Scheme 4: Nickel-catalyzed Suzuki coupling of 3-chloro-2-methoxycarbonly benzo[b]thiophene)

The nickel-based method has effective activation of C-Cl bond, resulting in the coupling of benzothiophene with phenylboronic acid in the presence of 5 mol%  $NiCl_2(dppe)$  and 2.0 equivalents of  $K_3PO_4$  in boiling toluene. The product was further applied to the palladium-catalyzed decarboxylative arylation.

#### 1.2.2. Iron-catalyzed Suzuki coupling

In 2009, Darcel reported a cross-coupling reaction of halogenoaryl compounds (X = I, Br) with aryl boronic acid in ethanol with catalytic amount of  $FeCl_3$  and stoichiometric amount of KF (Scheme 5).<sup>14</sup>

$$R' = Br, I$$

$$K = Br, I$$

$$K = (HO)_2 B$$

$$R' = \frac{FeCl_3 (10 \text{ mol}\%)}{KF (3 \text{ equiv.})}$$

$$R' = \frac{FeCl_3 (10 \text{ mol}\%)}{KF (3 \text{ equiv.})}$$

(Scheme 5: Iron-catalyzed Suzuki coupling of aryl bromide and aryl iodide) Many catalysts are formed by heavy or rare metals and their toxicity and expensive prices are the major concerns for large-scale industrial production. Iron is one of the most abundant metals on the earth and it is inexpensive and environmental friendly.

#### 1.2.3. Palladium-catalyzed Suzuki coupling

Palladium-catalyzed cross-coupling is versatile and highly effective for reactions like amination,<sup>15</sup> Heck reaction,<sup>16</sup> Hiyama coupling<sup>17</sup> and Suzuki coupling. However, there

are several disadvantages of using palladium catalyst system, such as high cost, toxicity and the potential contamination of the products.<sup>18</sup> The applications are limited in the massive large-scale industrial production, especially in the pharmaceutical industry which have to closely monitor the metal contamination of products. Despite the disadvantages, the effectiveness, efficiency and wide substrates availability outweigh the disadvantages of using palladium for catalytic reaction.

There are countless journals about the palladium-catalyzed Suzuki coupling. Aryl iodides,<sup>19</sup> bromides,<sup>20</sup> triflates<sup>21</sup> and chlorides are commonly used for electrophilic partners. In 2004, Buchwald and co-workers reported SPhos for the palladium-catalyzed Suzuki coupling of sterically hindered aryl bromides and aryl chlorides (Scheme 6 and 7).<sup>22</sup>



(Scheme 6: Palladium-catalyzed Suzuki coupling of aryl bromides using SPhos)



(Scheme 7: Palladium-catalyzed Suzuki coupling of aryl chloride using SPhos) In fact, aryl tosylates and aryl mesylates which are relatively inert than aryl halides

can also be used as effective electrophile partners (Scheme 8 and 9).<sup>23,24</sup>



(Scheme 8: Palladium-catalyzed Suzuki coupling of aryl mesylates using CMphos)



(Scheme 9: Palladium-catalyzed Suzuki coupling of aryl tosylates using CMphos) Different electrophilic partners for Suzuki coupling is continuously explored since the Suzuki coupling is considered as one of the most effective methods for the construction of C (sp<sup>2</sup>)-C(sp<sup>2</sup>) linkages. It is noteworthy for chemists to have further exploration of Palladium-catalyzed Suzuki-Miyaura coupling.

#### **1.3 Phosphine ligands for Suzuki coupling**

The development of phosphine ligands plays an important role of transition-metal-catalyzed reactions. The steric and electronic properties of phosphines could have a lot of variation and modification. This allows the fine-tuning of the coordinated species and the enhancement of desired properties of the complex at different steps of catalytic cycle.<sup>25</sup> Phosphine ligands can stabilize and improve the reactivity of catalyst.<sup>26</sup>

# 1.3.1. Examples of reported phosphine ligands for Suzuki coupling

Many research groups reported ligands which associated with palladium to perform the Suzuki coupling in low catalytic loading and at high product yield. For example, Buchwald and co-workers had reported a series of biarylmonophosphine which are highly effective for the coupling of a wide range of aryl halides.<sup>27</sup> (Figure 2) Beller's group had reported the use of pyrrole as the scaffold.<sup>28</sup> (Figure 2). Hartwig's group used the ferrocenyl-based dialkylphosphines for cross-coupling.<sup>29</sup> (Figure 2)



Buchwald group R = Cy, R', R'', R''' = i-Pr (XPhos) R = Cy, R', R'' = MeO, R''' = H (S-Phos) R = t-Bu, R', R'', R''' = H (JohnPhos) R =Cy, R', R'', R''' = H (CyJohnPhos)



(Figure 2: Recent development of phosphine ligands having aryl groups) Besides, some ligands had simpler design on their structure. For example, the Fu and

Koie group had reported a tri-tert-butylphosphine ligand.<sup>30</sup>

#### P(t-Bu)<sub>3</sub> Fu and Koie group

(Figure 3: Recent development of phosphine ligands having alkyl substituents)

The reported ligands for Suzuki coupling share the same feature that most of them

consist of a phosphorus atom which binds to the metal atom during catalysis.<sup>31</sup> Those

phosphine ligands can be further classified into two categories according to their

structural characteristics. For ligands in figure 1, phosphines having aryl groups at an appropriate position are fixed by their spacers.<sup>32</sup> The other category of phosphine ligands bear three alkyl substituents.(Figure 3) Recently, the dialkylphosphine ligands dominate because of their bulkiness and electron-richness.

#### 1.3.2. Rationale of dialkylphosphine-ligand design

In order to understand the ligand design, the general structure of Buchwald group's ligand was demonstrated:



(Figure 4: Using Buchwald group as an example of ligand's design) The alkyl group attached to phosphorus atom plays an important role of determining the electron density on phosphine.<sup>33</sup> The electron density on phosphine is critical for catalysis since the phoshphine binded to the metal center donates the electron to the  $\sigma$ \* orbital of C-X bond to undergo the oxidative addition. In addition, the size of alkyl groups can facilitate the reductive elimination. Most of the reported ligands consisted of dicyclohexylphosphine or ditert-butylphosphine, since they are relatively bulky and electron rich.<sup>34</sup>

The upper aryl ring increases the size of ligand that can stabilize the ligand during catalysis and facilitate the reduction elimination.<sup>35</sup> Substituted groups, R<sub>4</sub>, can be

added to fine-tune the electronic density on phosphorus atom or further increase the size of ligand.<sup>36</sup>

The lower aryl ring is used to allow the stabilization of Pd-arene interaction<sup>37</sup> and increase the size of ligand, resulting in faster reductive elimination.

The basic rationale of designing a ligand is the same, however, we are able to generate different type of ligands with a lot of variations, such as changing the scaffold, dialkylphosphine or substituted groups on the ligands.

#### **1.4 Examples of P,O-typed phosphine ligands**

P,O-type ligands are a kind of mixed-donor ligands consisting hard and soft donor atoms. They are a class of hemilabile ligands in which a hard (O) and soft (P) atoms bind to the metal in opposite manner.<sup>38</sup> The hard atom, O, binds to hard metal with strong coordination while the interaction between the hard metal and soft donor atom, P, is relatively weak (Figure 5).



(Figure 5: Comparison of binding mode towards hard and soft metal)

The situation is vice versa for soft metal. The weakly coordinated atom can be easily

dissociated whenever demanded and could exert a dynamic "on and off" mechanism.<sup>39</sup> This property is highly tunable and contributes to generate vacant site for the coordination of substrate and the donor atoms can provide unique reactivity to the metal complexes.<sup>40</sup>

The diversities of the P,O-type ligands are wide that the ligands can couple with different group, such as acetyl group, sulfonyl group and amido group. And its electronic properties and steric properties can be fine-tuned by changing the substituted group on the aryl ring and the bottom group.

#### 1.4.1. P,O-type ligands with acetyl group

In 1999, Guram/Bei et al. from Symyx Technologies reported a P,O-type ligands with acetyl group for Suzuki-Miyaura cross-coupling reactions of aryl chlorides.<sup>41</sup> The ligand was prepared from 2'-bromoacetophenone and 2'-bromobenzaldehyde which are commercially available (Scheme 10).



(Scheme 10: Synthesis of hemilabile ligand with acetyl group)

When the R group is methyl, the ligand is effective to the construction of the C-N bond coupling reactions through the amination of aryl chloride.<sup>42</sup>

#### 1.4.2. P,O-type ligands with sulfonyl group

In 2004, Singer/Tom et al. from Pfizer reported a new sulfone type ligand which contained a hemilabile sulfonyl oxygen and a dialkylphosphino group.<sup>43</sup>



(Scheme 11: Synthesis of P,O-type ligand with sulfonyl group)

The mono-phosphine ligands were prepared by one step through ortho-metallation in which commercially available phenylsulfone or substituted diarylsulfones react with *n*-BuLi and followed by the addition of the chlorodialkylphosphines (Scheme 11). The ligand is effective to the amination of aryl bromide.

#### 1.4.3. P,O-type ligands with amido group

In 2004, Kwong reported P,O-type ligands with amido group which are highly effective for Suzuki-Miyaura coupling of aryl chloride and amination of unactivated aryl chloride.<sup>44</sup> Those ligands are directly synthesized from commercially available *N,N*-diethylbenzamide (Scheme 12) through ortho-lithiation protocol which was explored by Beak and Snieckus.<sup>45</sup>



(Scheme 12: Synthesis of P,O-type ligand with amido group)

When the R groups are Cy or t-Bu, the biaryl product formed in excellent yield with low catalyst loading at  $60^{\circ}$ C.

#### 1.4.4. Indolyl phosphine ligands

In 2008, Kwong's research group reported a new family of highly tunable indolyl phosphine ligands.<sup>46</sup>



(Scheme 13: Synthesis of indolyl phsophine ligand)

The ligand was highly effective in Suzuki-Miyaura cross-coupling of both aryl and heteroaryl chlorides with aryl boronic acid and the Pd-catalyst loading can be down to 0.01%. The coupling of deactivated chlorides with aryl boronic acid provided good yield with moderate catalyst loading.



TABLE 1: Palladium-Catalyzed Suzuki-Miyaura Coupling of ArCl<sup>a</sup>

<sup>*a*</sup> Reaction conditions: ArCl (1.0 mmol), Ar'B(OH)<sub>2</sub> (1.5 mmol), K<sub>3</sub>PO<sub>4</sub> • H<sub>2</sub>O (3.0 mmol), Pd(OAc)<sub>2</sub>/L = 1:3, and THF (3.0 mL) were stirred for 24 h at 100 °C under nitrogen. <sup>*b*</sup> Isolated yields. <sup>c</sup>Reaction conditions: ArCl (1.0 mmol), *n*-BuB(OH)<sub>2</sub> (2.0 mmol), K<sub>3</sub>PO<sub>4</sub> • H<sub>2</sub>O (3.0 mmol), Pd(OAc)<sub>2</sub>/L = 1:3, and toluene (3.0 mL) were stirred for 24 h at 100 °C under nitrogen.

#### **1.5 Summary**

Suzuki coupling is applicable in many fields, such as pharmaceutical industries and polymer, and it is one of the most effective methods of constructing carbon-carbon bond. It is noteworthy that chemists research on the improvement and expansion of the scope of Suzuki coupling. There are countless journals reported the palladium-catalyzed Suzuki coupling. Apart from the metal, ligands play an important role in the cross-coupling. Recently, the reported ligands for Suzuki coupling are mainly bulky and electron-rich dialkylphosphine ligands. These ligands are highly effective since they can facilitate both oxidative addition through electron-richness and reductive elimination through bulkiness of ligands.

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#### **Chapter 2**

# The study of electronic effects towards the reactivity of indolyl phosphine ligands

#### **2.1. Introduction**

In 2008, our research group published a journal about an indolyl phosphine ligand which is highly effective for the Suzuki coupling of aryl chlorides with arylboronic acid.<sup>1</sup> As an extension of our continuous interest in the ligand, we have been interested in studying the electronic effects towards the reactivity of the ligands. For designing a phosphine ligand, the presence of electron-rich phosphine enhances the rate of oxidative addition while the bulkiness of ligand size increases the rate of reductive elimination.<sup>2</sup> In theory, the reactivity of a ligand is directly proportional to electron density at phosphorus atom.<sup>3</sup>

A series of 5-substituted indolyl phosphine ligands were prepared for the comparison of the electronic effect towards the reactivity of ligand. The purpose of this research is to contribute to the future development and modification of phosphine ligands and to demonstrate the importance of altering the electron density on phosphorus atom by the addition of either electron-donating or electron-withdrawing groups towards the overall reactivity of phosphine ligands.

#### 2.2 Results and discussion

# 2.2.1. Synthesis of a series of 5-substituted indolyl phosphine ligands

Based on our previous success of developing indolyl phosphine ligand, ligand **2**, which is highly effective for the Suzuki-Miyaura Coupling of aryl chlorides, we synthesized a series of 5-substituted indolyl phosphine ligands in order to test the effect of the electronic effect towards the reactivity of the P,O-type ligand.<sup>4</sup>



(Scheme 1: Synthesis of a series of 5-substituted indolyl phosphine ligands) By altering the substituted groups on the 5' position on the indole ring, the electron density on phosphorus atom could be changed.<sup>5</sup> All the 5-substituted indoles are commercially available and inexpensive, except the 5-phenyl indole.<sup>6</sup>

For precursor **1f**, it could not be effectively abstracted by directed ortho- metalation (DoM) using *n*-BuLi,<sup>7</sup> since the C-Br will be cleaved before the deprotonation of the 2'position of indole ring, resulting in the addition of  $PCy_2$  into the 5'position of indole ring.



Figure 1. Reaction pathway for precursor 1f

Since lithiation proceeded under  $-78^{\circ}$ C,<sup>8</sup> kinetic control pathway will dominate and product 1 will be the major product. Therefore, the precursor **1f** was used for the synthesis of 5-phenyl precursor via the coupling of precursor **1f** with phenyl boronic acid.<sup>9</sup> (Scheme 2)



(Scheme 2: Synthesis of 5-phenyl indolyl phosphine ligand)

0	5	1 0		
Ligand	R	Precursor (% yield)	Ligand (% yield)	<sup>31</sup> P NMR
2	Н			-22.132
2a	F	52	56	-21.563
<b>2b</b>	Cl	70	79	-21.635
2c	CF <sub>3</sub>	85	50	-21.786
2d	MeO	88	69	-21.835
2e	CH <sub>3</sub>	69	67	-25.199
<b>2f</b>	Ph	82	64	-21.904

Table 1: Ligands' yield and their corresponding <sup>31</sup>P NMR

Theoretically, the more electron donating substitute group leads to a more negative <sup>31</sup>P NMR chemical shift indicating the higher electron density on the phosphine atom. The electron donating effect should be expected as follow:

$$MeO > CH_3 > H > Cl > F > Phenyl > CF_3$$

However, the experimental results fail to show the expected trend of <sup>31</sup>P NMR. The possible reason is that the distance between the substituted group on 5' position of indole ring and the phosphorus atom is too far. Therefore, the electronic effect is not significant.

#### 2.2.2. Ligand screening

To compare the reactivity of a series of 5-substituted indolyl phosphine ligands, the coupling between the sterically hindered 2,6-dimethyl boronic acid and 4-chlorotoluene was used as the benchmark reaction. From our journal published in 2008, it showed that ligand **2** was able to perform the same reaction with 0.067% mol of  $Pd(OAc)_2$  to give 92% of desired product. To demonstrate the difference in reactivity between the 5-substituted phosphine ligands, the catalyst loading of the reaction was set to 0.025% mol of  $Pd(OAc)_2$ , so as to prevent the complete conversion of the starting material into product.

Me Cl +	Me Pd(C Pd(C He Me	025% Pd- <b>2</b> DAc) <sub>2</sub> , 1:3 M:L ( <sub>3</sub> PO₄ H <sub>2</sub> O THF, 24hr 100¢J	Me Me	$R \rightarrow PCy_2$ $R = H$ $2a, R = F$ $2b, R = CI$ $2c, R = CF_3$ $2d, R = MeO$ $2e, R = Me$ $2f, R = Ph$
entry	Ligand	R	Conversion % <sup>a</sup>	% yield of product <sup>a</sup>
1	2	Н	77	76
2	2a	F	61	54
3	<b>2b</b>	Cl	49	43
4	2c	CF <sub>3</sub>	42	36
5	2d	MeO	82	82
6	2e	Me	80	80
7	<b>2f</b>	Ph	78	55

Table 2: The reactivity of a series of 5-substituted indolyl phosphine ligands

<sup>a</sup> GC yield were repeated, average of two trials and using dodecane as internal standard.

The result showed that 5-MeO indolyl phosphine ligand has the highest reactivity among the other 5-substituted ligands. It is reasonable that the phosphine atom of 5-MeO ligand is the most electron-rich and the ligand can effectively donate electron to  $\sigma$  \* orbital of C-Cl, resulting in faster oxidative addition.<sup>10</sup> However, the difference in the reactivity is not obvious for the substituted ligands containing electron-donating groups at the 5' position of the indole ring. The reactivity for ligand **2**, **2d** and **2e** are 76%, 82% and 80% respectively. It is probably because the ligand **2** without substituted group is already electron-rich enough to cleave the C-Cl bond. Further enhancing the electron density on the phosphine atom has slight improvement on the reactivity of the indolyl phosphine ligand.

However, the addition of the electron-withdrawing group on the indole ring has
significant inhibition on the reactivity of the indolyl phosphine ligands. From the table, the reactivity for ligand 2c is only 36% which is less than the half of ligand 2 containing no substitution on the indole ring. The reactivity for other substituted ligands containing electron-withdrawing group ranged between 43% and 55%. Our finding showed the importance of the electron density on the phosphorus atom towards the reactivity of a ligand. For many cross coupling, such as amination,<sup>11</sup> Heck reaction,<sup>12</sup> oxidative addition is one of the rate-determining step<sup>13</sup> and it depends on the amount of the electron available for donation to anti-bonding orbital of electrophile.



Figure 2. X-Ray structure of ligand 2d, 5-MeO indolyl phosphine ligand

# 2.2.3. Synthesis of a family of 5-MeO indolyl dialkylphosphine ligands

After the discovery of the 5-MeO indole as a better scaffold, we synthesize a family of 5-MeO indolyl phosphine ligands to find out the best dialkylphosphine for that scaffold.

Table 3: The percentage yield of a series of 5-MeO indolyl dialkylphosphine ligands



## 2.2.4. Phosphino moiety screening

To test the effectiveness of the 5-MeO ligands, the previous benchmark reaction was used to compare their reactivity.

Table 4: The reactivity of a series of 5-MeO indolyl dialkylphosphine ligands



entry	Ligand	R	Conversion% <sup>a</sup>	% yield of product <sup>a</sup>
1	2d	Су	82	82
2	<b>2g</b>	t-Bu	37	32
3	2h	i-Pr	54	48
4	2i	Ph	trace	trace

<sup>a</sup> GC yield were repeated, average of two trials and using dodecane as internal standard. The table showed that the dicyclohexylphosphino analogue was the best partner for the 5-MeO scaffold. The highest catalytic activity for ligand **2d** may be explained by the electron richness of the cyclohexylphosphine.<sup>14</sup> Ligand **2i** with diphenylphosphino moiety had almost no reactivity while ligand **2g** bearing a sterically congested and electron-donating di-*tert*-butylphosphino has lower reactivity than the half of ligand **2d**.<sup>15</sup> Ligand **2h** having di-isopropyl phosphino showed a better reactivity than ligand **2g**. After finding out the ligand **2d** as the best ligand among the others, a wide range of activated and deactivated aryl chlorides were coupled with arylboronic acid in order to show the substrate scopes and demonstrate the reactivity towards various substrates combination, using the same optimized reaction conditions.

# 2.2.5. Palladium-Catalyzed Suzuki-Miyaura Coupling of both activated and deactivated aryl chlorides

Compared to ligand **2** having no substituted group on the ring, ligand **2d** has slight improvement in using lower catalytic loading to perform the coupling of same substrates (Table 5).



Table 5: Palladium-Catalyzed Suzuki-Miyaura Coupling of ArCl<sup>a</sup>



<sup>a</sup> Reaction conditions: ArCl (1.0 mmol), Ar'B(OH)<sub>2</sub> (1.5 mmol), K<sub>3</sub>PO<sub>4</sub> • H<sub>2</sub>O (3.0 mmol), Pd(OAc)<sub>2</sub>/L = 1:3, and THF (3.0mL) were stirred for 24 h at 100°C under nitrogen. <sup>b</sup> Isolated yields.

For the coupling of deactivated aryl chlorides, entry 1-4, the catalyst loading ranged from 0.033%-0.05% mol of Pd. Apart from the deactivated aryl chlorides, the ligand **2d** was able to catalyze the coupling of activated aryl chlorides bearing function groups, such as keto, aldehyde, ester and nitriles, with extremely low catalyst loading ranging from 0.01% to 0.05%. Most of the coupling reactions could be generally performed with 0.01% catalyst loading. The presence of functional groups weakened the strength of C-Cl bond, resulting in the requirement of extremely low catalyst loading. For entry 5, the proton on the 1' position of indole ring could be tolerated during the catalysis and the catalyst loading and product yield were satisfactory.

## 2.2.6. Palladium-Catalyzed Suzuki-Miyaura Coupling of

## heteroaryl chlorides

In addition, ligand **2d** was highly effective for coupling of heteroaryl chlorides with arylboronic acid and the catalyst loading could be generally down to 0.01% mol Pd. (Table 6)

MeO B(OH)<sub>2</sub> PCy<sub>2</sub> 0.01-0.02% Pd-**2d**  $R^1$ K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O C THF **100**℃ Ligand 2d Entry %yield<sup>b</sup> Product ArCl  $Ar'B(OH)_2$ Mol% Pd Me Me 11 0.02 93 B(OH)<sub>2</sub> Me CI 0.01 12 97 B(OH)<sub>2</sub> Мe B(OH)<sub>2</sub> CI 0.01 13 94 OMe CI 14 0.01 95 B(OH)<sub>2</sub> ÓМе

Table 6: Palladium-Catalyzed Suzuki-Miyaura Coupling of Heteroaryl Chlorides<sup>a</sup>



<sup>a</sup> Reaction conditions: ArCl (1.0 mmol), Ar'B(OH)<sub>2</sub> (1.5 mmol), K<sub>3</sub>PO<sub>4</sub> • H<sub>2</sub>O (3.0 mmol), Pd(OAc)<sub>2</sub>/L = 1:4, and THF (3.0mL) were stirred for 24 h at 100°C under nitrogen. <sup>b</sup> Isolated yields.

The optimal reaction conditions for the coupling of heteroaryl chlorides were the same, except the ratio of metal to ligand. The ratio was set at 1 to 4 and more ligand was required to compete the vacant sites of Palladium metal with substrates. The lone pair electron of nitrogen atom in heteroaryl chlorides was able to bind with the metal. Therefore, more ligands were required to force the substrate out from the metal and occupy the vacant sites on metal.

## **2.3 Conclusion**

In summary, we have synthesized a series of 5-substituted indolyl phosphine ligands to study the electronic effect towards the reactivity of P,O-type ligand. From our research, it revealed that the addition of electron-donating group on the 5'position on indole ring could enhance the electron density on phosphorus atom and resulted in the slight improvement of the reactivity of ligand. However, the introduction of electron-withdrawing group would greatly inhibit the reactivity of ligand. The research finding will be an important reference for the future development of phosphine ligands and it showed the importance of the electron density on phosphorus atom which plays an important role of the oxidative addition during the catalysis. We anticipate that we can apply the principle into our future ligands' design and modification.

## **2.4 Experimental section**

General Procedure for Suzuki-Miyaura Coupling of aryl chlorides: Pd(OAc)<sub>2</sub> (2.3 mg, 0.010 mmol) and ligand (0.030 mmol) were loaded into an oven-dried Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen for three times. Precomplexation was applied by adding freshly distilled THF into the tube. The solution was stirred for about 1 to 2 minutes until all the metal and ligand were dissolved in the solvent. Aryl chlorides (1.0 mmol), arylboronic acid (1.5 mmol), and K<sub>3</sub>PO<sub>4</sub> • H<sub>2</sub>O (3.0 mmol) were loaded into another Schlenk tube, and the system was further evacuated and flushed with nitrogen three times. The solvent THF (2.0 ml) was added, following the addition of catalyst dissolved in THF. The total volume of THF in the catalytic system is 3ml. The tube was stirred at room temperature for several minutes and then placed into a preheated oil bath (100 °C) for the time period as indicated in the tables. After completion of reaction as judged by GC analysis, the reaction tube was allowed to cool to room temperature and quenched with water and diluted with Ether. The organic layer was separated and the aqueous layer was washed with Ether twice. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

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## Chapter 3

## Newly Developed Benzimidazole-Based Phosphine Ligands for Palladium-Catalyzed Suzuki-Miyaura Coupling of Aryl Chlorides 3.1. Introduction

Continuing with the previous research of the synthesis of the indolyl phosphine ligands in 2008,<sup>1</sup> we further explore the use of benzimidazole as the scaffold of ligands. Benzimidazole is chosen since it is commercially available and reasonable priced. In addition, the precursors of ligands are easily deprotonated since there is only one proton at the 2' position of benzimidazole. During the synthesis of ligands, less side products will be formed, resulting in atom economy.<sup>2</sup> For modification, the reactivity of ligands can be modified by the addition of substituted groups into the benzimidazole ring.<sup>3</sup>

The research idea of using benzimidazole came from Matthias Bella, in 2004, who published the use of dialkylphosphinoimidazoles as new ligands for Suzuki Miyaura coupling of aryl chlorides with general catalyst loading 0.05 mol%Pd<sup>4</sup> and however, the metal to ligand ratio is too high (1:10). *N*-Arylbenzimidazoles were prepared by a copper-catalyzed *N*-arylation of benzimidazole. The obtained *N*-arylated benzimidazoles were then deprotonated by a mixture of *n*-BuLi and TMEDA in *n*-hexane or THF (Scheme 1).



(Scheme 1: Synthesis of *N*-aryl-2-(dialkylphosphino)benzimidazoles)

From the idea of Beller, we combine the benzimidazole, hemilabile *N*,*N*-diisopropyl carbamoyl group and dialkylphosphino group together to generate a series of newly developed benzimidazole-based phosphine ligands. The ligands were applied to the Suzuki-Miyaura coupling of aryl chlorides.



**Figure 1.** Strategic design of an easily diversified phosphine ligand family

Literature reports concerning the use of benzimidazole as ligands' scaffold are limited.<sup>5</sup> Therefore the use of benzimidazole for the synthesis of ligand will be a new direction and there will be a lot of room to explore.

## **3.2. Results and Discussion**

### 3.2.1. Preparation of ligands



(Scheme 2: General picture of the synthesis of a family of benzimidazole-based phosphine ligands)

The synthesis of the benzimidazole-based phosphine ligands was a two-step process. The starting materials, benzimidazole or 5,6-dimethyl benzimidazole, were reacted with the *N*,*N*-diisopropylcarbomyl chloride through condensation reaction. Then the purified precursors were lithiated by *n*-BuLi under  $-78^{\circ}$ C,<sup>6</sup> following the trapping of dialkylphosphine to generate various ligands.<sup>7</sup> (Scheme 2) The yields of precursor and

ligand were	shown as	follow:
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	0		1 0	
Entry	Ligand	Precursor %	Ligand %	Chemical shift of
		yield	yield	<sup>31</sup> P NMR
1	2a		73	-15.95
2	<b>2b</b>		67	-7.66
3	2c	87	65	14.35
4	2d		58	-25.44

Table 1: Ligands' yield and their corresponding <sup>31</sup>P NMR

5	2e		52	-28.99
6	<b>2f</b>	N/A	60	-22.55
7	2g		65	-24.34
8	2h		56	-16.35
9	2i		57	-8.07
10	2j		48	13.95
11	2k	75	42	-25.66
12	21		77	-39.43
13	2m		62	-19.70

## 3.2.2. Ligands screening

Table 2: Investigation on the effectiveness of the benzimidazolylphosphine ligands 2 in Suzuki-Miyaura coupling of nonactivated  $\text{ArCl}^a$ 



entry	ligand	%yield <sup>b</sup>
1	<b>2a</b> (R' = H, R'' = C(O)N <i>i</i> -Pr <sub>2</sub> , R = Cy)	43
2	<b>2b</b> (R' = H, R'' = C(O)N <i>i</i> -Pr <sub>2</sub> , R = <i>i</i> -Pr)	18
3	<b>2c</b> (R' = H, R'' = C(O)N <i>i</i> -Pr <sub>2</sub> , R = $t$ -Bu)	8
4	<b>2d</b> ( $R' = H, R'' = C(O)Ni-Pr_2, R = Ph$ )	0
5	$2e (R' = H, R'' = C(O)Ni - Pr_2, R = Et)$	0
6	2f(R' = H, R'' = Me, R = Cy)	18
7	2g(R' = H, R'' = Me, R = Pentyl)	9
8	<b>2h</b> (R' = Me, R'' = C(O)N <i>i</i> -Pr <sub>2</sub> , R = Cy)	57
9	<b>2i</b> ( $R' = Me, R'' = C(O)Ni-Pr_2, R = i-Pr$ )	23
10	<b>2j</b> (R' = Me, R'' = C(O)N <i>i</i> -Pr <sub>2</sub> , R = <i>t</i> -Bu)	13
11	<b>2k</b> (R' = Me, R'' = C(O)N <i>i</i> -Pr <sub>2</sub> , R = Ph)	0
12	<b>2l</b> (R' = Me, R'' = C(O)N <i>i</i> -Pr <sub>2</sub> , R = $o$ -Toly)	0
13	<b>2m</b> ( $R' = Me, R'' = C(O)Ni-Pr_2, R = Pentyl)$	38

<sup>&</sup>lt;sup>a</sup> Reaction conditions: ArCl (1.0 mmole), PhB(OH)<sub>2</sub> (1.5 mmole), K<sub>3</sub>PO<sub>4</sub> • H<sub>2</sub>O (3.0 mmole),

 $Pd(OAc)_2/L = 1:2$ , and THF (3 mL) were stirred for 24 h at 100°C under nitrogen. <sup>b</sup> Calibrated GC yields were reported using dodecane as the internal standard.

The coupling between 2-chlorotoluene and phenyl boronic acid was applied as benchmark reaction for the comparison of the ligands' reactivity. The reaction conditions were fixed to use 0.05 mol% of  $Pd(OAc)_2$  with metal to ligand ratio 1:2, together with  $K_3PO_4 \cdot H_2O$  as base and THF as solvent.

From the table 2, ligand **2h** and **2a** showed the greatest and the second greatest reactivity respectively among the other ligands. The possible reasons were that dicyclohexylphosphino moiety was sufficiently electron-rich to facilitate the donation of electron from phosphine atom to the C-Cl bond.<sup>8</sup> In addition, the bulky size of dicyclohexylphosphino moiety enhanced the rate of reductive elimination.<sup>9</sup>

During oxidative addition, the electron was donated to the  $\sigma^*$  orbital of C-Cl bond for cleavage.<sup>10</sup> The more electron density on phosphine atom, the faster should be the rate of oxidative addition.<sup>11</sup> Ligand **2h** having dimethylbenzimidazole as scaffold had further enhancement of the electron density on the phosphine atom, resulting in faster reactivity than ligand **2a**.



**Figure 2.** X-Ray structure of ligand **2a**, Benzimidazole-based dicyclohexylphosphine ligand



**Figure 3.** X-Ray structure of ligand **2h**, Dimethylbenzimidazole-based dicyclohexylphosphine ligand

Ligand 2c and 2j both bearing a sterically congested and electron-donating di-*tert*-butylphosphino moiety showed very low product yield towards coupling reaction.<sup>12</sup> Ligand 2b and 2i both bearing diisopropylphosphino moiety with similar steric bulkiness as dicyclohexylphosphino moiety afforded lower conversion. Ligand 2d and 2k with a diphenylphosphino moiety provided no conversion. It is probably because the  $\pi$ -conjugated system in two phenyl rings decreased the electron richness in coordinated metal center by delocalization. In addition, ligand 2e bearing a less sterically congested diethylphosphino moiety showed no conversion.

By comparing the ligands 2a and 2f, replacing the carbamoyl group by methyl group would greatly inhibit the catalytic activity. This direct comparison demonstrated the importance of the bulky carbamoyl group which acted as a main role of on and off mechanism<sup>13</sup> and probably enhanced the rate of reductive elimination.

## 3.2.3. The effect of the addition of dimethyl group on scaffold

		-					
	Ligand	Ligand $\delta$ of		Ligand	$\delta$ of	$0/mald^a$	
	(R'=H)	<sup>31</sup> P NMR	70yleid	(R' = Me)	<sup>31</sup> P NMR	70yleiu	
R = Cy	2a	-15.95	43	2h	-16.35	57	
R = i-Pr	2b	-7.66	18	2i	-8.07	23	
R = t-Bu	2c	14.35	8	2j	13.95	13	
R = Ph	2d	-25.44	0	2k	-25.66	0	

Table 3: Direct comparison of the effectiveness between ligands 2a-d and 2h-k with various dialkylphosphino moiety

<sup>a</sup> Calibrated GC yields were reported using dodecane as the internal standard.

In order to further enhance the catalytic activity of the newly developed benzimidazole-based phosphine ligands, fine-tuning was made on the scaffold by incorporating two methyl groups to the 5,6-position of benzimidazole.<sup>14</sup> From table 3, it showed that there was a general enhancement of reactivity among various dialkylphosphino moiety when using 5,6-dimethyl benzimidazole as scaffold. The enhancement of the electron density on phosphine atom was evidenced by the <sup>31</sup>P NMR of ligands.<sup>15</sup> The chemical shifts of <sup>31</sup>P NMR of ligands **2h-k** were more up-field (value were shifted to negative side) than ligands **2a-d** (Table 2).

## 3.2.4. Reaction condition screening

Table 4: Optimization of the reaction conditions of ligand  $2h^a$ 



entry	Pd source	Pd:L	mol% Pd	base	solvent	temp. °C	% vield <sup>b</sup>
1	$Pd_2(dba)_3$	1:2	0.05	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	THF	100	44
2	$Pd(OAc)_2$	1:2	0.05	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	THF	100	57
3	$Pd(dba)_2$	1:2	0.05	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	THF	100	31
4	PdCl <sub>2</sub>	1:2	0.05	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	THF	100	0
5	$Pd(OAc)_2$	1:1	0.05	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	THF	100	14
6	$Pd(OAc)_2$	1:2.5	0.05	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	THF	100	67
7	$Pd(OAc)_2$	1:3	0.05	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	THF	100	75
8	$Pd(OAc)_2$	1:4	0.05	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	THF	100	34
9	$Pd(OAc)_2$	1:5	0.05	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	THF	100	32
10	$Pd(OAc)_2$	1:10	0.05	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	THF	100	11
11	$Pd(OAc)_2$	1:3	0.05	K <sub>3</sub> PO <sub>4</sub>	THF	100	55
12	$Pd(OAc)_2$	1:3	0.05	K <sub>2</sub> CO <sub>3</sub>	THF	100	62
13	$Pd(OAc)_2$	1:3	0.05	Na <sub>2</sub> CO <sub>3</sub>	THF	100	28
14	$Pd(OAc)_2$	1:3	0.05	$Cs_2CO_3$	THF	100	4

15	$Pd(OAc)_2$	1:3	0.05	CsF	THF	100	2
16	$Pd(OAc)_2$	1:3	0.05	NaO(t-Bu)	THF	100	0
17	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	Dioxane	100	35
18	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	Toluene	100	17
19	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	t-Butanol	100	13
20	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	THF	r.t.	0
21	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	THF	90	28
22	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	THF	110	93
23	$Pd(OAc)_2$	1:3	0.1	$K_3PO_4 \cdot H_2O$	THF	100	91

<sup>*a*</sup> Reaction conditions: ArCl (1.0 mmole), PhB(OH)<sub>2</sub> (1.5 mmole), base (3.0 mmole), and solvent (3 mL) were stirred for 24 h under nitrogen. <sup>*b*</sup> Calibrated GC yields were reported using dodecane as the internal standard.

In the screening table, several reaction parameters were screened, such as metal source, metal to ligand ratio, base, solvent, temperature and catalyst loading. During the optimization, only one parameter was varied while keeping others constant. The parameter with the highest percentage yield would be chosen for further screening.

#### Effect of metal source:

Pd(OAc)<sub>2</sub> gave the best performance towards coupling reaction (Table 4, entries 1-4) among the other metal sources. Pd<sub>2</sub>(dba)<sub>3</sub> and Pd(dba)<sub>2</sub> are Pd(0) metal sources which require no initial reduction step (entries 1 and 3), but the dissociation of dba is difficult that less vacant site on Pd(0) will be available for ligand binding.<sup>16</sup> Therefore, they are not an effective metal source. Besides, PdCl<sub>2</sub> provided no conversion because PdCl<sub>2</sub> is insoluble towards the solvent.<sup>17</sup> Pd(OAc)<sub>2</sub> was selected as the metal source for further investigations. In addition, Pd(OAc)<sub>2</sub> offers a competitive edge that it is relatively air-stable than Pd<sub>2</sub>(dba)<sub>3</sub> and Pd(dba)<sub>2</sub>.

#### Effect of metal to ligand ratio:

From entry 2 and entries 5-10, there was an increasing trend of the product yield when the metal to ligand ratio increased from 1:1 to 1:3. After the optimal ratio, 1:3, the product yield was inversely proportional to the metal to ligand ratio. The product yield was greatly suppressed when the ratio was up to 1:10. The possible reason was that excess amount of ligand might block the coordination of the substrate with the metal during the beginning of metallic cycle, resulting in ineffective catalyst system.<sup>18</sup> The 1:3 ratio was found to be the most suitable metal to ligand ratio for the optimum reactivity of ligand **2h**.

#### Effect of base:

Seven bases were chosen for comparison and the result revealed that weak bases, such as  $K_3PO_4 \cdot H_2O$  (entry 10),  $K_3PO_4$  (entry 11),  $K_2CO_3$  (entry 12),  $Na_2CO_3$ , (entry 13),  $Cs_2CO_3$  (entry 14), gave better reactivity than the strong base, CsF (entry 15) and NaO(t-Bu) (entry 16). Base plays an important role in transmetallation.<sup>19</sup> Among the weak bases,  $K_3PO_4 \cdot H_2O$  showed the best performance.

#### Effect of solvent:

THF, toluene, dioxane and DMF have different boiling points and solubilities towards the substrates. The unique performance of the solvents is based on the principle of solvent effect.<sup>20</sup> By various solvents surveyed, THF was found to be the most effective solvent for ligand 2h to coupling aryl chlorides with aryl boronic acid.

#### Effect of temperature:

The reactivity of the ligand increased with the temperature and the reactivity was the highest when the temperature was 110°C (entry 22). If there is no heat energy applied to the catalysis, the conversion of the coupling reaction was almost zero (entry 20). Heat is an essential factor for coupling reaction to assist the substrate to overcome the activation barrier.

#### Effect of catalyst loading:

The conversion of the coupling reaction was directly proportional to the amount of the catalyst. However, the catalyst loading should be kept as low as possible while the conversion should be over 90%. The amount of catalyst used reflected the difficulty of coupling of different substrates. In the screening test, 0.05% mol Pd was used to compare the conversion under different reaction conditions. If the catalyst loading was too high or too low, the difference between various reaction conditions was not obvious.

#### Inter-play between temperature and catalyst loading

For entry 22 and entry 23, both had above 90% product yield. The differences between two entries were the catalyst loading and the temperature that low catalyst loading with high temperature produced similar performance as high catalyst loading with low temperature. From economic aspect, we had to consider the cost of metal and the cost of temperature. In addition, when we had chosen the use of high temperature, there will be more flexible in adjusting the catalyst loading for other coupling partners. Therefore, 110°C was selected for our further investigation.

## 3.2.5. Suzuki-Miyaura coupling of both activated and

## deactivated ArCl

Table 5: Palladium-Catalyzed Suzuki-Miyaura Coupling of Aryl Chlorides with Arylboronic  $Acids^a$ 



entry	ArCl	Ar'B(OH) <sub>2</sub>	Product	mol% Pd	%yield <sup>b</sup>
1 <sup>c</sup>	Me		Me	0.1%	91
2	CI	(HO) <sub>2</sub> B		0.05%	93
3	OMe	(HO) <sub>2</sub> B		0.067	96
4	OMe CI	Me (HO) <sub>2</sub> B	OMe Me	0.1	86
5	MeO	Me (HO) <sub>2</sub> B	MeO Me	0.1	97



<sup>*a*</sup> Reaction conditions: ArCl (1.0 mmole), Ar'B(OH)<sub>2</sub> (1.5 mmole), K<sub>3</sub>PO<sub>4</sub> • H<sub>2</sub>O (3.0 mmole), Pd(OAc)<sub>2</sub>/L = 1:3, and THF (3 ml) were stirred for 24 h at 110°C under nitrogen. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> At 100°C

A range of aryl chlorides were examined under the preliminary optimized reaction conditions (Table 5). The deactivated aryl chlorides containing different substituted groups, such as methyl and methoxy group, were coupled with different arylboronic acids. In the presence of moderate catalyst loading, 0.05-0.1 mol% Pd, sterically hindered aryl chlorides were coupled with arylboronic acids to give excellent product yields (Table 5, entries 2-5). Upon examining the methyl group and methoxy group at the *ortho*-position of the aryl chlorides coupling, a higher catalyst loading was required for 2-chloroanisole substrate (Table 5, entries 2 and 3). Although methoxy group provided less steric hindrance than methyl group, methoxy group provided stronger electronic effect than methyl group to strengthen the C-Cl bond. In this case, the electronic effect became a predominant factor, so higher catalyst loading was required.

On the other hand, when increasing the steric hindrance of arylboronic acids, a higher catalyst loading should be applied to obtain an excellent yield (Table 5, entries 3 and 4). By comparing the effect of different position of methoxy groups, the methoxy group at *para*-position showed higher isolated yield due to less steric hindrance (Table 5, entries 4 and 5). In order to further extend the scope of this new ligand, a highly steric hindred substrate was studied (Table 5, entry 6), however it only had 44% yield at 0.5 mol% catalyst loading.

Apart from the study in deactivated substrates, the substrates which consisted of functional groups such as keto, aldehyde, ester, and nitriles were compatible under the reaction conditions. The catalyst loading of 0.01-0.05 mol% of Pd was achieved

(Table 5, entries 7-12). Ligand **2h** could couple the aryl chlorides with activated functional groups and give excellent yields under very low catalyst loading. Generally, there was different reactivity of the substrates when the functional group at either *para-* or *meta-* position (Table 5, entries 8 and 9). Compared with entry 9, the keto group at *para-* position (entry 8) showed higher electron-withdrawing effect towards the C-Cl bond, resulting in higher catalytic activity.<sup>21</sup>

Among these activated aryl chlorides, electrophilic substrates having aldehyde and ester groups showed the highest reactivity and required the lowest catalyst loading, which could be down to 0.01 mol% Pd (Table 5, entries 10 and 11).

## 3.2.6. Suzuki-Miyaura coupling of Hetero-ArCl

Table 6: Palladium-Catalyzed Suzuki-Miyaura Coupling of Heteroaryl Chlorides with Aryl or Alkylboronic Acids<sup>*a*</sup>







<sup>*a*</sup> Reaction conditions: Het-ArCl (1.0 mmole), Ar'B(OH)<sub>2</sub> (1.5 mmole),  $K_3PO_4 \bullet H_2O$  (3.0 mmole),  $Pd(OAc)_2/L = 1:3$ , and THF (3 mL) were stirred for 24 h at 110°C under nitrogen. <sup>*b*</sup> Isolated yields. C Reaction conditions: ArCl (1.0 mmole), *n*-BuB(OH)<sub>2</sub> (2.0 mmole),  $K_3PO_4 \bullet H_2O$  (3.0 mmole),  $Pd(OAc)_2/L = 1:3$ , and toluene (3 mL) were stirred for 24 h at 110°C under nitrogen.

Apart from functionalized aryl chlorides, the coupling of heteroaryl chlorides were also examined. The results showed that the heteroaryl chlorides were an effective substrates for Suzuki-Miyaura coupling with extremely low catalyst loading ranged from 0.02-0.067 mol% Pd (Table 5). The reactivity of the chloropyridine was mainly dependent on the position of chloro group on the pyridine ring. According to the catalyst loading, the reactivity of 2-chloropyridine was greatly higher than that of 3-chloropyridine. (Table 6, entries 1 and 3).

In addition, preliminary study in the coupling of alkylboronic acid with aryl chloride was successful (Table 6, entry 4). The optimized reaction conditions were modified by increasing the alkylboronic acid ratio to two equivalents and changing the solvent to toluene since the alkylboronic acid is more readily oxidized to stable alkane species and toluene is an optimal solvent for the coupling due to solvent effects. Notably, it showed that this catalyst system could tolerate against  $\beta$ -H elimination with moderate catalyst loading.

## **3.3.** Conclusion

A family of newly developed benzimidazole-based phosphine ligands has been reported. The ligands are highly tunable by changing the dialkylphosphine group and can be further fine-tuned by adding dimethyl group into the scaffold. The optimal ligand **2h** among the family is highly effective for Suzuki-Miyaura coupling of both activated and deactivated aryl chlorides and also heteroaryl chlorides. Some of them catalyzed the reaction under an extremely low catalyst loading which can be down to 0.01 mol% of palladium. Further exploration and versatility of this hemilabile P,O-type ligand will be attainable.

## **3.4 Experimental section**

General Procedure for Suzuki-Miyaura Coupling of aryl chlorides: Pd(OAc)<sub>2</sub> (2.3 mg, 0.010 mmol) and ligand (0.030 mmol) were loaded into an oven-dried Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen for three times. Precomplexation was applied by adding freshly distilled THF into the tube. The solution was stirred for about 1 to 2 minutes until all the metal and ligand were dissolved in the solvent. Aryl chlorides (1.0 mmol), arylboronic acid (1.5 mmol), and K<sub>3</sub>PO<sub>4</sub> • H<sub>2</sub>O (3.0 mmol) were loaded into another Schlenk tube, and the system was further evacuated and flushed with nitrogen three times. The solvent THF (2.0 ml) was added, following the addition of catalyst dissolved in THF. The total volume of THF in the catalytic system is 3ml. The tube was stirred at room temperature for several minutes and then placed into a preheated oil bath (100 °C) for the time period as indicated in the tables. After completion of reaction as judged by GC analysis, the reaction tube was allowed to cool to room temperature and quenched with water and diluted with Ether. The organic layer was separated and the aqueous layer was washed with Ether twice. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

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## Chapter 4 Summary

In conclusion, the addition of electron donating group on the scaffold could fine-tune and improve the overall reactivity of ligands. The possible reason was due to the enhancement of electron density on phosphorous atom, resulting in the faster rate of oxidative addition. But on the other hand, the addition of electron withdrawing group would inhibit the overall reactivity of ligands. The study of electronic effect towards the overall reactivity of phosphine ligands will contribute the further development and modification of related phosphine ligands.

Combined with the idea of previous research, the benzimidazole-based phosphine ligands' reactivity could be enhanced by adding two dimethyl groups into the scaffold. The optimal ligand was highly effective for Suzuki-Miyaura coupling of both activated and deactivated aryl chlorides and also heteroaryl chlorides. Some entries had an extremely low catalyst loading down to 0.01 mol% of palladium.

## Appendix

#### **Chapter 2: Supporting data of precursors and ligands**

#### Synthesis of 1-(5-fluoro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1a)



General procedures for condensation reaction:

5-fluoro-1H-indole (4.05g, 30.0 mmol) was dissolved in 40ml THF in dropping funnel and added dropwisely to the 60ml THF solution contained 1.2 equiv NaH (60% in mineral oil, 1.44g, 36.0 mmol) at 0°C. NaH was washed with hexane (20 ml  $\times$  3) under N<sub>2</sub>. The mixture stirred for 1 h at room temperature. After recooling to 0 °C 1.4 equiv N,N-diisopropylcarbamoylchloride (6.87g, 42.0 mmol) dissolved in 40 ml THF are added to the mixture dropwisely and the mixture is stirred at room temperature over night. Solvent was removed by vacuum. DCM 300 ml and water 100 ml was added to the mixture and the organic phase was separated. The remaining water phase was further extracted with 200 ml DCM twice. The combined organic phase was washed with brine and concentrated. The concentrated mixture was applied to  $3 \times 3$  cm silca pad and eluted with dichloromethane. The organic solvent was dried evaporated over Na<sub>2</sub>SO<sub>4</sub> and in vacuum. The white powder of 1-(5-fluoro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (4.10g, 52%) was obtained after column chromatography. Melting point: 63.2-65.1°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.42 (d, *J* = 6.8Hz, 12H), 3.78-3.85 (m, 2H), 6.54-6.55 (m, 1H), 7.00-7.05 (m, 1H), 7.23-7.29 (m, 2H), 7.62-7.65 (m, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  21.0, 48.5, 104.5, 105.5, 105.6, 105.8, 111.1, 111.4, 113.7, 126.6, 129.3, 129.4, 132.4, 152.3, 157.3, 159.7(Complex unresolved C-P splitting was observed); IR (cm<sup>-1</sup>) 3131.32, 3110.65, 2994.49, 1971.33, 2935.55, 2875.94, 1674.75, 1619.67, 1515.39, 1434.22, 1376.11, 1337.46, 1264.53, 1157.10, 1080.37, 949.60, 876.67; MS (EI): *m/z* (relative intensity) 262 (M<sup>+</sup>, 26), 204 (2), 176 (2), 162 (10), 135 (43), 128 (54), 107 (20), 86 (100), 70 (9); HRMS: calcd. for C<sub>15</sub>H<sub>19</sub>N<sub>2</sub>OFH<sup>+</sup>: 263.1560, found 263.1562.

### <u>Synthesis of 1-(2-(dicyclohexylphosphino)-5-fluoro-1H-indol-1-yl)-</u> 2-isopropyl-3-methylbutan-1-one (2a)

General procedures for ligand synthesis:

1-(5-fluoro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.32g, 5.0 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under nitrogen atmosphere. The solution was cooled to -78 °C in dry ice/acetone bath. Titrated n-BuLi (5.5 mmol) was added dropwise by syringe. After the reaction mixture was stirred for an hour at -78°C, chlorodicyclohexylphosphine (1.33ml, 6.0 mmol) dissolved in 5 ml THF was added dropwise by syringe. The reaction was allowed to
warm to room temperature and stirred overnight. Solvent was removed under vacuum. After the solvent was removed under vacuum, the crude product was applied to column chromatography and the pure product was then dried under vacuum. White solid of title compound (1.28g, 56%) was obtained. Melting point: 157.3-159.4 $^{\circ}$ C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.24-1.92 (m, 34H), 3.42 (bs, 2H), 6.70 (s, 1H), 6.95-7.00 (m, 1H), 7.21-7.28 (m, 2H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) δ 20.5, 21.0, 26.2, 27.1, 29.9, 30.0, 30.1, 33.7, 104.8, 105.0, 105.1, 109.4, 109.5, 110.7, 110.9, 111.0, 128.1, 128.2, 133.4, 133.5, 136.7, 136.9, 151.3, 157.0, 159.3 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -21.56; IR (cm<sup>-1</sup>) 2965.45, 2931.72, 1686.18, 1618.06, 1499.50, 1359.63, 1259.18, 1135.02, 1108.38, 1027.03, 848.36, 780.13; MS (EI): *m/z* (relative intensity) 458 (M<sup>+</sup>, 10), 415 (53), 375 (100), 333 (27), 293 (7), 245 (17), 198 (17), 166 (40), 135 (8), 86 (13); HRMS: calcd. for C<sub>27</sub>H<sub>40</sub>N<sub>2</sub>OFPH<sup>+</sup>: 459.2941, found 459.2956.



General procedures for the synthesis of precursor 1a were followed. 5-chloro-1H-indole (4.55g, 30.0 mmol), NaH (1.44g, 36.0 mmol), and

1b

2b

N,N-diisopropylcarbamoylchloride (6.87g, 42.0 mmol) were used to afford 1-(5-chloro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (5.86g, 70%) as white solid compound. Melting point: 100.14-102.7°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.42 (d, J = 6.4Hz, 12H), 3.76-3.83 (m, 2H), 6.54 (t, J = 3.2 Hz, 1H), 7.22-7.28 (m, 2H), 7.58-7.63 (m, 2H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  21.0, 48.6, 104.0, 104.1, 113.7, 113.8, 120.0, 120.1, 123.2, 123.3, 126.3, 126.4, 126.8, 129.9, 134.2, 152.0(Complex unresolved C-P splitting was observed); IR (cm<sup>-1</sup>) 3004.42, 2971.01, 2929.10, 1677.15, 1435.52, 1377.49, 1300.77, 1265.20, 1157.52, 1124.16, 1064.72, 1013.29, 898.52; MS (EI): m/z (relative intensity) 278 (M<sup>+</sup>, 25), 178 (8), 151 (33), 128 (63), 116 (8), 86 (100), 70 (8); HRMS: calcd. for C<sub>15</sub>H<sub>19</sub>N<sub>2</sub>OClH<sup>+</sup>: 279.1264, found 279.1267.

# <u>Synthesis of 1-(5-chloro-2-(dicyclohexylphosphino)-1H-indol-1-yl)-</u> 2-isopropyl-3-methylbutan-1-one (2b)

General procedures for the synthesis of ligand 2a were followed. 1-(5-chloro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.40g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodicyclohexylphosphine (1.33ml, 6.0 mmol) were used afford 1-(5-chloro-2-(dicyclohexylphosphino)-1H-indol-1-yl)-2-isopropylto 3-methylbutan-1-one (1.87g, 79%) as white solid compound. Melting point: 169.1-171.7°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.24-1.99 (m, 34H), 3.46-3.51 (m, 2H),

6.68 (s, 1H), 7.15-7.30 (2H), 7.59-7.64 (m, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) δ 20.6, 21.1, 26.2, 27.1, 29.9, 30.0, 33.7, 109.0, 111.1, 119.6, 122.7, 126.0, 128.8, 135.1, 136.5, 136.7, 151.0(Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>) δ -21.64; IR (cm<sup>-1</sup>) 2989.71, 2928.64, 2846.80, 1696.66, 1488.94, 1435.63, 1369.74, 1156.60, 1062.24, 1000.20, 887.15, 783.41, 710.60, 650.26, 552.20; MS (EI): *m/z* (relative intensity) 474 (M<sup>+</sup>, 10), 431 (45), 391 (100), 349 (23), 309 (8), 276 (8), 261 (18), 225 (16), 198 (27), 182 (36); HRMS: calcd. for C<sub>27</sub>H<sub>40</sub>N<sub>2</sub>OClPH<sup>+</sup>: 475.2645, found 459.2651.

# <u>Synthesis of 1-(5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-</u> <u>3-methylbutan-1-one (1c)</u>



General procedures for the synthesis of precursor 1a were followed. 5-(trifluoromethyl)-1H-indole (1.35g, 7.5 mmol), NaH (0.33g, 8.25 mmol), and N,N-diisopropylcarbamoylchloride (1.48g, 9.0 mmol) were used to afford 1-(5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.99g, 85%) as orange solid compound. Melting point: 77.4-78.1°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.45 (d, J = 6.9Hz, 12H), 3.79-3.82 (m, 2H), 6.69 (d, J = 3.3Hz, 1H), 7.31 (t, J = 5.5Hz, 1H), 7.54 (d, J = 7.7Hz, 1H), 7.77 (d, J = 8.7Hz, 1H), 7.94 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  21.1, 48.7, 105.2, 113.0, 118.4, 118.5, 119.9, 123.6, 123.7, 123.9, 126.4, 126.8, 128.3, 137.3, 139.6, 151.9 (Complex unresolved C-P splitting was observed); IR (cm<sup>-1</sup>) 3003.73, 2978.69, 1681.65, 1527.18, 1432.48, 1263.69, 1217.01, 1108.12, 1014.71, 886.35, 748.95, 611.16; MS (EI): m/z (relative intensity) 312 (M<sup>+</sup>, 18), 293 (2), 254 (2), 226 (2), 212 (9), 185 (41), 166 (10), 158 (5), 145 (2), 137 (5), 128 (73), 86 (100); HRMS: calcd. for C<sub>16</sub>H<sub>19</sub>N<sub>2</sub>OF<sub>3</sub>H<sup>+</sup>: 313.1528, found 313.1531.

# <u>Synthesis of 1-(2-(dicyclohexylphosphino)-5-(trifluoromethyl)-1H-indol-1-yl)-</u> 2-isopropyl-3-methylbutan-1-one (2c)

followed. General procedures for the synthesis of ligand 2a were 1-(5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.56g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodicyclohexylphosphine (1.33ml, 6.0 mmol) were used to afford 1-(2-(dicyclohexylphosphino)-5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.27g, 50%) as white solid compound. Melting point: 191.1-192.5°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.91-2.20 (m, 34H), 3.31-3.61 (m, 2H), 6.85 (s, 1H), 7.39-7.48 (m, 2H), 7.95 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) δ 20.3, 20.7, 20.8, 21.0, 26.2, 26.5, 26.8, 27.2, 27.3, 27.4, 28.9, 29.0, 30.1, 30.2, 30.4, 33.7, 110.3, 110.5, 118.1, 118.2, 119.1, 122.7, 123.0, 123.8, 126.5, 127.2, 137.4, 137.6, 138.0, 150.8 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz,

CDCl<sub>3</sub>) δ -21.79; IR (cm<sup>-1</sup>) 2977.00, 2958.31, 2927.14, 2873.91, 2846.83, 1696.73, 1471.67, 1445.82, 1314.46, 1265.22, 1205.15, 1113.02, 1027.84, 999.35, 896.09, 854.49, 793.66, 649.30; MS (EI): *m*/*z* (relative intensity) 508 (M<sup>+</sup>, 7), 489 (6), 465 (74), 425 (100), 383 (27), 343 (7), 315 (6), 301 (22), 259 (20), 241 (6), 216 (30), 198 (29), 166 (7), 117 (6), 86 (9), 55 (10); HRMS: calcd. for C<sub>28</sub>H<sub>40</sub>N<sub>2</sub>OF<sub>3</sub>PH<sup>+</sup>: 509.2909, found 509.2914.

Synthesis of 2-isopropyl-1-(5-methoxy-1H-indol-1-yl)-3-methylbutan-1-one (1d)



General procedures for the synthesis of precursor 1a were followed. 5-methoxy-1H-indole (4.42g, 30.0 mmol), NaH (1.44g, 36.0 mmol), and N,N-diisopropylcarbamoylchloride (6.87g, 42.0 mmol) were used to afford 2-isopropyl-1-(5-methoxy-1H-indol-1-yl)-3-methylbutan-1-one (7.23g, 88%) as white solid compound. Melting point: 68.7-69.3°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.43 (d, *J* = 6.6Hz, 12H), 3.82-3.88 (m, 2H), 3.89 (s, 3H), 6.53 (d, *J* = 3.6Hz, 1H), 6.93-6.96 (m, 1H), 7.09 (d, *J* = 2.5Hz, 1H), 7.19 (d, *J* = 3.5Hz, 1H), 7.62 (d, *J* = 8.9Hz, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.9, 21.0, 48.3, 55.5, 102.5, 104.4, 112.7, 113.5, 125.6, 129.4, 130.8, 152.5, 154.9, 155.0 (Complex unresolved C-P splitting was observed); IR (cm<sup>-1</sup>) 3002.71, 2968.38, 1674.96, 1618.62, 1507.67, 1434.68, 1313.60, 1273.83, 1213.67, 1113.93, 1077.73, 859.84, 722.37, 603.68; MS (EI): *m/z* (relative intensity) 274 (M<sup>+</sup>, 67), 216 (2), 188 (2), 174 (17), 159 (2), 147 (17), 135 (38), 128 (54), 117 (5), 104 (17), 86 (100), 76 (8); HRMS: calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>H<sup>+</sup>: 275.1760, found 275.1770.

# <u>Synthesis of 1-(2-(dicyclohexylphosphino)-5-methoxy-1H-indol-1-yl)-</u> 2-isopropyl-3-methylbutan-1-one (2d)

General procedures synthesis of ligand 2a followed. for the were 2-isopropyl-1-(5-methoxy-1H-indol-1-yl)-3-methylbutan-1-one (1.37g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodicyclohexylphosphine (1.33ml, 6.0 mmol) were used to afford 1-(2-(dicyclohexylphosphino)-5-methoxy-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.62g, 69%) as white solid compound. Melting point: 142.3-142.9°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.24-1.92 (m, 34H), 3.43-3.52 (m, 2H), 3.87 (d, J = 10.7 Hz, 1H), 6.67 (s,1H), 6.89 (d, J = 6.6 Hz, 1H), 7.08 (d, J = 2.2 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.23 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.3, 20.5, 20.7, 20.8, 26.3, 26.5, 27.1, 27.2, 28.9, 29.0, 29.2, 29.8, 30.0, 30.1, 33.8, 55.6, 101.4, 109.3, 109.4, 111.1, 113.0, 128.3, 132.2, 135.1, 135.3, 151.7, 154.6 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -21.84; IR (cm<sup>-1</sup>) 2995.22, 2929.82, 2851.00, 1685.57, 1618.68, 1501.43, 1470.83, 1427.35, 1370.59, 1361.22, 1272.26, 1226.83, 1163.70, 1119.92, 1002.58, 852.63, 830.40, 792.24; MS (EI): m/z (relative intensity) 470 (M<sup>+</sup>, 9), 427 (38), 387 (100), 370 (2), 345 (26), 305 (6), 272 (34), 257 (24), 221 (8), 203 (6), 178 (51), 147 (16), 112 (8), 86 (16), 55 (14); HRMS: calcd. for C<sub>28</sub>H<sub>43</sub>N<sub>2</sub>O<sub>2</sub>PH<sup>+</sup>: 471.3140, found 471.3150.

Synthesis of 2-isopropyl-3-methyl-1-(5-methyl-1H-indol-1-yl)butan-1-one (1e)



General procedures for the synthesis of precursor 1a were followed. 5-methyl-1H-indole (3.93g, 30.0 mmol), NaH (1.44g, 36.0 mmol), and N,N-diisopropylcarbamoylchloride (6.87g, 42.0 mmol) were used to afford 2-isopropyl-3-methyl-1-(5-methyl-1H-indol-1-yl)butan-1-one (5.34g, 69%) as orange solid compound. Melting point: 75.7-77.1°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.43 (d, *J* = 6.8Hz, 12H), 2.49 (d, *J* = 9.3Hz, 3H), 3.81-3.86 (m, 2H), 6.52 (d, *J* = 3.4Hz, 1H), 7.11-7.19 (m, 2H), 7.42 (s, 1H), 7.59 (d, *J* = 8.4Hz, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  21.0, 21.2, 21.3, 48.4, 104.2, 112.4, 120.4, 124.6, 125.2, 129.1, 130.5, 134.1, 152.7 (Complex unresolved C-P splitting was observed); IR (cm<sup>-1</sup>) 2971.14, 2929.45. 1671.10, 1430.03, 1375.29, 1325.89, 1215.27, 1157.23, 1013.60, 897.36, 721.71, 649.78, 612.28, 546.84, 514.97, 468.57, 429.99; MS (EI): m/z (relative intensity) 258 (M<sup>+</sup>, 58), 200 (2), 185 (1), 172 (2), 158 (18), 143 (2), 130 (63), 117 (2), 103 (11), 86 (100), 77 (11); HRMS: calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>OH<sup>+</sup>: 259.1810, found 259.1809.

# <u>Synthesis of 1-(2-(dicyclohexylphosphino)-5-methyl-1H-indol-1-yl)-</u> 2-isopropyl-3-methylbutan-1-one (2e)

General procedures for the synthesis of ligand 2a were followed. 2-isopropyl-3-methyl-1-(5-methyl-1H-indol-1-yl)butan-1-one (1.29g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodicyclohexylphosphine (1.33ml, 6.0 mmol) were used to afford 1-(2-(dicyclohexylphosphino)-5-methyl-1H-indol-1-yl)-2-isopropyl-

3-methylbutan-1-one (1.52g, 67%) as white solid compound. Melting point: 162.3 -163.1°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.44-1.76 (m, 30H), 1.95 (m, 2H), 2.31-2.33 (m, 2H), 2.47 (s, 3H), 3.48-3.53 (m, 2H), 6.69 (s, 1H), 7.04 (d, *J* = 9.0 Hz, 1H), 7.22 (d, *J* = 8.4Hz, 1H), 7.40 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.5, 20.8, 21.2, 21.3, 25.6, 26.0, 26.3, 26.4, 26.7, 30.6, 30.8, 37.1, 37.4, 37.5, 37.8, 48.5, 48.7, 108.7, 108.8, 110.0, 119.8, 119.9, 120.2, 124.1, 128.2, 129.6, 135.0, 135.1, 137.5, 137.7, 151.8 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$ -25.20; IR (cm<sup>-1</sup>) 2975.02, 2923.11, 2846.57, 1685.16, 1430.89, 1311.37, 1267.48, 1206.19, 1159.83, 1133.40, 1114.15, 1026.36, 1000.90, 866.46, 828.54, 794.85; MS (EI): *m/z* (relative intensity) 454 (M<sup>+</sup>, 7), 411 (51), 371 (100), 354 (2), 342 (5), 329
(29), 289 (6), 256 (32), 241 (40), 205 (15), 187 (6), 162 (71), 131 (25), 112 (6), 86
(25); HRMS: calcd. for C<sub>28</sub>H<sub>43</sub>N<sub>2</sub>OPH<sup>+</sup>: 455.3191, found 455.3208.

## Synthesis of 1-(5-bromo-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1f)



General procedures for the synthesis of precursor 1a were followed. 5-bromo-1H-indole (3.84g, 20.0 mmol), NaH (0.88g, 22.0 mmol), and N,N-diisopropylcarbamoylchloride (3.94g, 24.0 mmol) were used to afford 1-(5-bromo-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (5.09g, 79%) as white solid compound. Melting point: 95.1-96.5°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.44 (t, *J* = 6.7Hz, 12H), 3.79-3.84 (m, 2H), 6.54 (d, *J* = 3.9Hz, 1H), 7.21 (d, *J* = 3.8Hz, 1H), 7.38 (d, *J* = 6.9Hz, 1H), 7.58 (d, *J* = 8.7Hz, 1H),7.76 (d, *J* = 1.8Hz, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.9, 48.5, 103.9, 114.2, 114.3, 123.2, 125.8, 126.2, 130.4, 134.5, 151.9 (Complex unresolved C-P splitting was observed); IR (cm<sup>-1</sup>) 3004.69, 2928.17, 1667.24, 1428.10, 1323.96, 1214.03, 1157.37, 1084.06, 896.29, 818.94, 717.24, 687.95, 636.27, 576.76, 470.49, 428.01; MS (EI): m/z (relative intensity) 322 (M<sup>+</sup>, 20). 264 (1), 238 (1), 224 (4), 195 (17), 168 (2), 157 (2), 143 (4), 128 (82), 115 (17), 86 (100), 70 (9); HRMS: calcd. for C<sub>15</sub>H<sub>19</sub>N<sub>2</sub>OBrH<sup>+</sup>: 323.0759, found 323.0769.

## Synthesis of N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide (1g)



Precursor **1g** is synthesized by the coupling between precursor **1f** and phenyl boronic acid through Suzuki-Miyaura Coupling. 1-(5-bromo-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.61g, 5.0 mmol), phenyl boronic acid (7.5 mmol), and K<sub>3</sub>PO<sub>4</sub>H<sub>2</sub>O (3.42g, 15.0 mmol), with 1.0 mol% Pd(OAc)<sub>2</sub>, 3.0 mol% ligand **2d** and 15ml THF under 100°C were used to afford N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide (2.12g, 82%) as white solid compound. Melting point: 95.1-96.5°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.46 (d, *J* = 6.5Hz, 12H), 3.86-3.89 (m, 2H), 6.67 (s, 1H), 7.27 (t, *J* = 1.0Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.3Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 7.7Hz, 2H), 7.79 (d, *J* = 8.6Hz, 1H), 7.87 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  21.1, 48.2, 104.9, 112.6, 112.9, 118.7, 119.1, 122.5, 122.7, 125.5, 126.4, 126.8, 127.1, 127.4, 128.2, 128.3, 129.3, 134.6, 135.3, 139.5, 141.8, 152.3, 154.2 (Complex unresolved C-P splitting was observed); MS (EI): *m/z* (relative intensity) 320 (M<sup>+</sup>, 49), 234 (2), 220 (10), 204 (2), 193 (42), 177 (3), 165 (24), 152 (3), 139 (5), 128 (66), 115 (3), 86 (100), 70 (3); HRMS: calcd. for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>OH<sup>+</sup>: 321.1967, found 321.1970.

# <u>Synthesis of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5-phenyl-</u> <u>1H-indole-1-carboxamide (2f)</u>

General procedures for the synthesis of ligand 2a were followed. N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide (4.89g, 15.0 mmol), n-BuLi (16.5 mmol), and chlorodicyclohexylphosphine (3.99ml, 18.0 mmol) were used to afford 2-(dicyclohexylphosphino)-N,N-diisopropyl-5-phenyl-1H-indole-

1-carboxamide (4.40g, 64%) as white solid compound. Melting point: 188.1-189.4°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.26-1.94 (m, 34H), 3.51 (m, 2H), 6.80 (s, 1H), 7.33-7.39 (m, 2H), 7.47 (t, *J* = 6.3Hz, 3H), 7.67 (d, *J* = 7.7Hz, 2H), 7.83 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.7, 21.0, 26.3, 27.2, 30.0, 30.1, 33.9, 110.1, 110.5, 118.7, 122.5, 126.3, 127.2, 128.4, 128.6, 134.1, 135.6, 135.8, 136.4, 142.2, 151.5 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -21.90; IR (cm<sup>-1</sup>) 2923.76, 2846.01, 1692.87, 1430.49, 1369.69, 1311.84, 1263.85, 1025.57, 763.24, 699.99; MS (EI): *m/z* (relative intensity) 516 (M<sup>+</sup>, 8), 473 (42), 433 (100), 391 (22), 351 (5), 318 (32), 303 (30), 267 (11), 249 (7), 224 (48), 193 (26), 165 (7), 112 (9), 86 (16), 55 (20); HRMS: calcd. for C<sub>33</sub>H<sub>45</sub>N<sub>2</sub>OPH<sup>+</sup>: 517.3348, found

## <u>Synthesis of 2-(di-tert-butylphosphino)-N,N-diisopropyl-5-methoxy-1</u> H-indole-1-carboxamide (2g)



ligand General for procedures the synthesis of 2a followed. were N,N-diisopropyl-5-methoxy-1H-indole-1-carboxamide (1.37g, 5.0 mmol), n-BuLi (5.5 mmol), and di-tert-butylchlorophosphine (1.14ml, 6.0 mmol) were used to afford 2-(di-tert-butylphosphino)-N,N-diisopropyl-5-methoxy-1H-indole-1-carboxamide (1.49g, 71%) as white solid compound. Melting point: 128.6-129.7°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.11-1.70 (m, 30H), 3.69 (m, 2H), 3.87 (s, 3H), 6.87-6.95 (m, 2H), 7.08 (d, J = 2.5Hz, 1H), 7.18-7.22 (m, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.8, 21.2, 30.5, 30.6, 32.8, 33.0, 48.5, 55.6, 101.6, 102.7, 104.5, 111.3, 111.7, 112.9, 113.3, 113.6, 125.7, 128.6, 129.5, 130.9, 132.2, 132.3, 136.0, 136.2, 151.2, 154.6, 155.1 (Complex unresolved C-P splitting was observed);  $^{31}$ P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$ 9.43; IR (cm<sup>-1</sup>) 2978.42, 2950.38, 2861.30, 1688.48, 1615.43, 1501.92, 1433.35, 1418.05, 1376.40, 1312.08, 1219.78, 1199.58, 1117.92, 1026.89, 869.22, 833.52, 800.47; MS (EI): *m/z* (relative intensity) 417 (M<sup>+</sup>, 1), 375 (2), 361 (100), 333 (2), 319

(9), 305 (5), 277 (5), 263 (19), 248 (2), 234 (5), 221 (11), 178 (17), 147 (5), 86 (5), 57

(7); HRMS: calcd. for  $C_{24}H_{39}N_2O_2PH^+$ : 419.2827, found 419.2840.

## <u>Synthesis of N,N-diisopropyl-2-(diisopropylphosphino)-5-methoxy-</u> 1H-indole-1-carboxamide (2h)



General procedures synthesis ligand followed. for the of 2a were N,N-diisopropyl-5-methoxy-1H-indole-1-carboxamide (1.37g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodiisopropylphosphine (0.96ml, 6.0 mmol) were used to afford N,N-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide (1.47g, 75%) as white solid compound. Melting point: 110.1-111.8°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.11-1.60 (m, 26H), 2.18 (s, 2H), 3.45-3.51 (m, 2H), 3.87 (s, 3H), 6.67 (d, J = 0.4Hz, 1H), 6.87-6.90 (m, 1H), 7.06 (d, J = 2.4Hz, 1H), 7.21 (d, J =8.8Hz, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) δ 19.7, 19.9, 20.6, 24.1, 55.7, 101.6, 109.3, 109.4, 111.1, 113.2, 128.3, 132.2, 132.3, 135.4, 135.6, 151.2, 154.6 (Complex unresolved C-P splitting was observed);  ${}^{31}$ P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -13.36; IR (cm<sup>-1</sup>) 2993.22, 2921.52, 2863.83, 1682.15, 1612.97, 1502.85, 1435.52, 1378.43, 1351.33, 1319.53, 1223.68, 1199.91, 1162.23, 1063.12, 1026.86, 872.68, 854.51,

794.90, 607.65; MS (EI): *m/z* (relative intensity) 390 (M<sup>+</sup>, 7), 347 (100), 305 (95), 290 (7), 279 (8), 263 (10), 220 (15), 203 (7), 189 (7), 178 (35), 147 (14), 135 (8), 86 (14); HRMS: calcd. for C<sub>22</sub>H<sub>35</sub>N<sub>2</sub>O<sub>2</sub>PH<sup>+</sup>: 391.2514, found 391.2499.





General procedures the followed. for synthesis of ligand 2a were N,N-diisopropyl-5-methoxy-1H-indole-1-carboxamide (1.37g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodiphenylphosphine (1.11ml, 6.0 mmol) were used to afford N,N-diisopropyl-5-methoxy-2-(diphenylphosphino)-1H-indole-1-carboxamide (1.49g, 65%) as white solid compound. Melting point: 186.1-187.4°C; <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.34 (d, J = 6.4Hz, 12H), 3.50-3.57 (m, 2H), 3.83 (s, 3H), 6.23 (s, 1H), 6.89-6.91 (m, 1H), 6.97 (d, J = 2.4Hz, 1H), 7.23 (d, J = 8.8Hz, 1H), 7.34-7.45 (m, 10H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) δ 20.6, 20.7, 21.2, 48.5, 48.8, 55.6, 55.7, 102.0, 111.3, 112.4, 113.6, 125.7, 128.3, 128.4, 128.5, 128.8, 133.1, 133.2, 133.4, 133.6, 135.9, 136.0, 136.7, 136.8, 151.2, 154.8 (Complex unresolved C-P splitting was observed): <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>) δ -27.76; IR (cm<sup>-1</sup>) 2958.58, 1686.05,

1616.61, 1471.19, 1432.60, 1369.15, 1318.06, 1165.12, 1118.11, 1061.10, 944.05, 910.07, 878.94, 742.26, 692.79, 610.08, 545.56, 501.42, 425.19; MS (EI): m/z (relative intensity) 458 (M<sup>+</sup>, 7), 415 (27), 373 (100), 360 (7), 347 (27), 331 (13), 314 (3), 299 (3), 286 (5), 272 (63), 257 (25), 238 (5), 223 (9), 209 (16), 183 (16), 86 (28); HRMS: calcd. for C<sub>28</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub>PH<sup>+</sup>: 459.2201, found 459.2216.

# Chapter 2: NMR spectrum and mass spectrum of precursors and ligands

<sup>1</sup>H NMR of 5-fluoro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



<sup>13</sup>C NMR of 5-fluoro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide





### Mass spectrum of 5-fluoro-N,N-diisopropyl-1H-indole-1-carboxamide

High resolution mass spectrum of 5-fluoro-N,N-diisopropyl-1H-indole-1-carboxamide

Liem	enta		npoortin	sin nope							raye
<b>Singl</b> Tolera Selec	l <b>e Ma</b> ance cted f	ass A = 5.0 filters:	<b>nalysis</b> ) PPM None	/ DBE:	min = -1	.5, max = 60	.0				
Monois 13 forn Elemer C: 0-15	sotopi nula(e nts Us 5 H:	ic Mas e) eval sed: 0-100	s, Even E uated with 0 N: 0-2	lectron lor h 1 results 2 O: 0-1	ns within limi F: 0-1	ts (all results (u	p to 1000) fo	r each mass	s)		
HR08_1	1202_1	11 (0.2	12) AM (Ce	n,4, 80.00, H	lt,10000.0,0.0	00,1.00); Sm (SG, 2 263	x3.00); Sb (15, .1562	10.00 ); Cm (8	:35)	то	F MS ES 1,10e
100											
100											
%											
%	249.	1594	254.2437	255.0628 2	257.2471	261.0539	264.1603 265.1506	266.1708 268.	<sup>1756</sup> 271.	274 1872 <sup>274.0857</sup>	.2746
%	249.	1594	254.2437 252.5	255.0628 2 255.0	257.2471 257.5	261.0539 260.0 262.5	264.1603 265.1506 5 265.0	266.1708 268. 267.5	<sup>1756</sup> 271. 270.0	274 1872 <sup>274.0857</sup> 272.5	.2746 m 
% 0 Minimu Maximu	249. 250 um: um:	1594	254.2437 252.5	255.0628 2 255.0 100.0	257.2471 257.5 0 5.0	261.0539 260.0 262.5 -1.5 60.0	264.1603 265.1506 3 265.0	266.1708 268. 267.5	1756 271. 270.0	274 1872 <sup>274.0857</sup> 272.5	.2746 m _275.0
%- 0 Minimu Maximu Mass	249. 250 um: um:	1594  Calc	254.2437 252.5 . Mass	255.0628 2 255.0 100.0 mDa	257.2471 257.5 5.0 PPM	261.0539 260.0 262.5 -1.5 60.0 DBE	264.1603 265.1506 265.0 i-FIT	266.1708 268. 267.5 Formula	1756 271. 270.0	274 1872 <sup>274.0857</sup> 272.5	.2746 m _275.0

## <sup>1</sup>H NMR of 2-(dicyclohexylphosphino)-5-fluoro-*N*,*N*-diisopropyl-1H-

indole-1-carboxamide



<sup>13</sup>C NMR of 2-(dicyclohexylphosphino)-5-fluoro-*N*,*N*-diisopropyl-1H-

indole-1-carboxamide



## <sup>31</sup>P NMR of 2-(dicyclohexylphosphino)-5-fluoro-*N*,*N*-diisopropyl-1H-

indole-1-carboxamide



High resolution mass spectrum of 2-(dicyclohexylphosphino)-5-fluoro-N,N-diisopropyl-1H-

## indole-1-carboxamide

Elemental Composition	on Report							Page	1
Single Mass Analysis Tolerance = 100.0 PPN Selected filters: None	И / DBE:	min = -1.5	5, max =	60.0					
Monoisotopic Mass, Even E 25 formula(e) evaluated witi Elements Used: C: 0-27 H: 0-1000 N: 0- Yeung chung Chiu, 6 HRDs 1202 6 97 (1 807) AM (Ce	lectron lons h 1 results with 2 O: 0-1 F	hin limits (al : 0-1 P: 0-	ll results (u -1 <sup>(0)</sup> : Sm (SG,	ip to 1000) 2x3.00); Sb (1	for each mass 5,10.00 ); Cm (8;	) 2:102)		TOF MS ES	5+
100 %			459.2956					2.23	e3
437.1971441.310	3 444.3065	453.1692	460.	2980 61.3020 466.	.3093 475.:	3166	481.2707	485.8209 m	1/z
435.0 440.0 Minimum: Maximum:	445.0 450	0 455.0	460.0 -1.5 60.0	465.0	470.0 475	.0	480.0	485.0	
Mass Calc. Mass	mDa	PPM	DBE	i-FIT	Formula				



## <sup>1</sup>H NMR of 5-chloro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide

<sup>13</sup>C NMR of 5-chloro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide





#### Mass spectrum of 5-chloro-N,N-diisopropyl-1H-indole-1-carboxamide

High resolution mass spectrum of 5-chloro-N,N-diisopropyl-1H-indole-1-carboxamide





<sup>1</sup>H NMR of 5-chloro-2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide

<sup>13</sup>C NMR of 5-chloro-2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide





<sup>31</sup>P NMR of 5-chloro-2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide

High resolution mass spectrum of 5-chloro-2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-

### indole-1-carboxamide

Elemental Composition F	Report		Page 1
Single Mass Analysis Tolerance = 100.0 PPM / Selected filters: None	DBE: min = -1.5, max	c = 60.0	
Monoisotopic Mass, Even Electr 25 formula(e) evaluated with 1 n Elements Used: C: 0-27 H: 0-1000 N: 0-2 C Yeung chung Chiu, 7	ron lons esults within limits (all result D: 0-1 P: 0-1 Cl: 0-1	s (up to 1000) for each mass)	
HR08_1202_7 16 (0.305) AM (Cen,4, 8	0.00, Ht,10000.0,0.00,1.00); Sm (\$ 475.265	SG, 2x3.00); Sb (15,10.00 ); Cm (10:19) i1	TOF MS ES+ 1.06e3
%- 453.1704 <sup>459.3033</sup> 4	63.2930 466.3120	477.2643 478.2656 479.2709 489.2975493.3790 497	.2463 499.2454 m/7
450.0 455.0 460.0	465.0 470.0 475.0	480.0 485.0 490.0 495.0	500.0
Minimum: Maximum:	-1.5 100.0 100.0 60.0		
Mass Calc. Mass	mDa PPM DBE	i-FIT Formula	
475.2651 475.2645	0.6 1.3 8.5	0.3 C27 H41 N2 O	P Cl



### <sup>1</sup>H NMR of 5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide







#### Mass spectrum of 5-(trifluoromethyl)-N,N-diisopropyl-1H-indole-1-carboxamide

High resolution mass spectrum of 5-(trifluoromethyl)-N,N-diisopropyl-1H-indole-1-carboxamide

Elemental Composition	n Report		Page 1
Single Mass Analysis Tolerance = 10.0 PPM Selected filters: None	/ DBE: min = -1	.5, max =	= 60.0
Monoisotopic Mass, Even Ele 62 formula(e) evaluated with Elements Used: C: 0-16 H: 0-1000 N: 0-2	ectron lons 1 results within limits O: 0-3 F: 0-3	(all results	s (up to 1000) for each mass)
Yeung Chung Chiu, C16N2OF3H19 HR08_1218_2 20 (0.379) AM (Cen, 100	4, 80.00, Ht,10000.0,0.00,	,1.00); Sm (S <sup>.</sup> 313.	iG, 3x2.00); Cm (9:26) TOF MS ES+ 1531 1.14e3
%			314.1568
0 303.2478 305.2667 304.0 306.0	307.2679 309.2037 308.0 310.0	312.1440 312.0	315.1578 316.6962 318.3005 320.2391 321.2384 m/z 314.0 316.0 318.0 320.0 322.0
Minimum: Maximum:	100.0 10.0	-1.5 60.0	
Mass Calc. Mass	mDa PPM	DBE	i-FIT Formula
313.1531 313.1528	0.3 1.0	6.5	0.1 C16 H20 N2 O F3

<sup>1</sup>H NMR of 2-(dicyclohexylphosphino)-5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-

indole-1-carboxamide



<sup>13</sup>C NMR of 2-(dicyclohexylphosphino)-5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



## <sup>31</sup>P NMR of 2-(dicyclohexylphosphino)-5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-

indole-1-carboxamide



High resolution mass spectrum of 2-(dicyclohexylphosphino)-5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide

	ientu											
Sing Toler Selec	rance rance	i <b>ss Analysi</b> = 5.0 PPM ilters: None	s /	DBE: mir	n = -1.5, m	ax = 50.	0					
Monoi Eleme C: 0-3 KIN-DE	isotopia mula(e ents Us 30 H: EPT-Y2 S IS ES+	c Mass, Even e) evaluated w sed: 0-45 N: 0-3 5032010 HS 1 41	Elect rith 1 O: 1 (0.76	ron lons results with 0-2 F: 0- 3) AM (Cen,10	in limits (up 3 P: 0-1 0, 80.00, Ar,50	to 50 close	est result 0); Sm (SC	ts for each G, 2x3.00); S	ı mass) b (10,10.0 509.	00 ); Cm (32 2914	:41)	2.84e4
1												
%										510.2953		
%	3	352.2502 360.328	7	397.1891	425.1819	453.7894	471.3136	481.1407	501.3263	510.2953	539.3008	m/z
%	340	352.2502 <sup>360.328</sup> 360	7 380	397.1891 400	425.1815 420	453.7894 440	471.3136	481.1407	501.3263 500	510.2953 511.3006 520	539.3008	m/z
%- 0	340 num : num :	352.2502 <sup>360.328</sup> 360	7 380	397.1891 400 5.0	425.1819 420 5.0	453.7894 440 -1.5 50.0	471.3136 460	481.1407 480	501.3263 500	510.2953 511.3006 520	539.3008 540	— m/z
% 0 tinim taxim	340 num : num :	352.2502 <sup>360.328</sup> 360 Calc. Mass	7 380	397.1891 400 5.0 mDa	425.1819 420 5.0 PPM *	453.7894 440 -1.5 50.0 DBE	471.3136 460 i-FIT	481.1407 480 Form	501.3263 500 nula	510.2953 511.3006 520	539.3008 540	m/z



## <sup>1</sup>H NMR of *N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide

<sup>13</sup>C NMR of *N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide





#### Mass spectrum of N,N-diisopropyl-5-methoxy-1H-indole-1-carboxamide

High resolution mass spectrum of N,N-diisopropyl-5-methoxy-1H-indole-1-carboxamide

Elementa	Composition	Report						Page 1
Single Ma Tolerance Selected f	<b>ss Analysis</b> = 100.0 PPM ilters: None	/ DBE:	min = -1	.5, max =	60.0			
Monoisotopi 10 formula(e Elements Us C: 0-16 H: Yeung chung C HR08_1202_4	c Mass, Even Ele e) evaluated with sed: 0-1000 N: 0-2 Chiu, 4 103 (1.919) AM (Cer	Ctron lons 1 results wit O: 0-2 0,4, 80.00, Ht,1	thin limits ( 	(all results (u ,1.00); Sm (SG 275.	up to 1000) fo , 2x3.00); Cm ( 1770	or each mass) 13:136)	т	OF MS ES+ 2.80e
100				274.2761				
%								
%-	7 268.9039 270	.8830 272.2	274.	1693	276.1799	77.1840	279.2321 280.2646	280.9063
% 0 268.188 268.0	7 268.9039 270 270.0	.8830 272.1 272.0	274. 2588	1693	276.1799 276.0	77.1840 278.0	279.2321 280.2646 280.0	280.9063
%- 0_268.188 268.0 Minimum: Maximum:	7 268.9039 270 270.0	.8830 272.3 272.0 100.0	274. 2588 _ 100.0	1693 274.0 -1.5 60.0	276.1799 2 276.0	77.1840 278.0	279.2321 280.2646 280.0	280.9063
% 0 268.188 268.0 Minimum: Maximum: Mass	7 268.9039 270 270.0 Calc. Mass	.8830 272.0 272.0 100.0 mDa	274. 2588 _ 100.0 _ PPM	1693 274.0 -1.5 60.0 DBE	276.1799 2 276.0 i-FIT	77.1840 278.0 Formula	279.2321 280.2646 280.0	280.9063



<sup>1</sup>H NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide

<sup>13</sup>C NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide





 $^{31} P \ NMR \ of \ 2-(dicyclohexylphosphino)-N, N-diisopropyl-5-methoxy-1 H-indole-1-carboxamide$ 

High resolution mass spectrum of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide

Liementai	Compositio	n Report					Page 1
Single Mas Tolerance = Selected fil	<b>s Analysis</b> = 5.0 PPM / ters: None	DBE: min	= -1.5, n	nax = 50.0			
Monoisotopic 190 formula(e Elements Use C: 0-30 H: 0 KIN-DEPT-Y1 50 TOF MS ES+	Mass, Even Ele e) evaluated with ed: )-45 N: 0-3 0 )32010 HS 1 39 (0.	ectron lons n 1 results with O: 0-2 F: 0-3 731) AM (Cen,10	nin limits (u P: 0-1 , 80.00, Ar,50	up to 50 close	st results for ea Sm (SG, 2x3.00); 471.3150	ach mass) Sb (10,10.00 ); Cm (3	3:39) 7.18e3
%-				*	472.3185		
338.3438	360.3260 371.1	998 397.1903	425.181	0 453.78	481.1426	501.3253	538.2679
338.3438 0 340	360.3260 371.1 360 38	1998 397.1903 30 400	425.181 420	0 453.78 440	481.1426 460 480	501.3253 500 520	538.2679 540
338.3438 0 340 Minimum: Maximum:	360.3260 371.1 360 38	1998 397.1903 30 400 5.0	425.181 420 5.0	0 453.78 440 -1.5 50.0	481.1426 42 160 480	501.3253 500 520	538.2679 
338.3438 0	360.3260 371.1 360 38 260 38	1998 397.1903 30 400 5.0 mDa	425.181 420 5.0 PPM	0 453.78 440 -1.5 50.0 DBE	481.1426 42 480 480 -FIT Fo	501.3253 500 520 rmula	538.2679 ,



<sup>1</sup>H NMR of *N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide







### Mass spectrum of N,N-diisopropyl-5-methyl-1H-indole-1-carboxamide

High resolution mass spectrum of N,N-diisopropyl-5-methyl-1H-indole-1-carboxamide

Elementa	I Compositio	n Report							Page
Single Ma Tolerance Selected f	ass Analysis = 50.0 PPM filters: None	/ DBE: m	in = -1.5	, max =	60.0				
Monoisotopi 12 formula( Elements U C: 0-16 H Yeung Chung QT_ESP_HR_	ic Mass, Even Ele e) evaluated with sed: : 0-1000 N: 0-3 Chiu, C16N20H22 WLM_2009_0720_2	ectron lons 1 results with O: 0-1 95 (1.794) AM (0	in limits (a Cen,4, 80.00	all results 0, Ht,10000. 259	(up to 1000) fo 0,0.00,1.00); Sm ( 9,1809	or each mass SG, 2x3.00); Cn	) n (48:96)	т	OF MS E 2.9
100									
%-	791				260.1844	07			
%245.0 0245.0	<sup>791</sup> 246.0806 0 247.5 25	250.9925 253 0.0 252.5	3.9457 256. 255.0	2696	260.1844 261.18 260.0 262	07 <sub>263.0782</sub> .5 265.0	<u>267.2657</u> 267.5	269.5508 270.0	272.26
%- 0 245.01 0 245.01 245.01 245.01 Minimum: Maximum:	<sup>791</sup> 246.0806 0 247.5 25	250.9925 253 0.0 252.5 100.0	3.9457 256. 255.0 50.0	2696 257.5 -1.5 60.0	260.1844 261.18 260.0 262	07 <u>263.0782</u> .5 265.0	267.2657 2 267.5	269.5508 270.0	272.26
%- 0 245.01 245.	791 246.0806 0 247.5 25 Calc. Mass	250.9925 253 0.0 252.5 100.0 mDa	3.9457 256 255.0 50.0 PPM	2696 257.5 -1.5 60.0 DBE	260.1844 261.18 260.0 262 i-FIT	07 <u>263.0782</u> .5 265.0 Formula	267.2657 267.5	269.5508 270.0	<u>272.26</u> 272.



<sup>1</sup>H NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide

<sup>13</sup>C NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide







High resolution mass spectrum of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide

	I Composition	n Report					Page 1
Single Ma Tolerance Selected	ass Analysis = 5.0 PPM / filters: None	DBE: mi	n = -1.5,	max = 50	.0		
Monoisotop 32 formula(i Elements U C: 0-30 H KIN-DEPT-Y3 TOF MS ES+	ic Mass, Even Ele e) evaluated with sed: : 0-45 N: 0-3 0 5032010 HS 1 39 (0.	ectron lons 1 results wit O: 0-2 P: 0 731) AM (Cen,	hin limits (u -1 10, 80.00, Ar,	up to 50 clo .5000.0,0.00,1	sest results fo .00); Sm (SG, 2×	or each mass) (3.00); Sb (10,10.0 (455.32	00 ); Cm (33:39) 08 2.90e3
%-						4	56.3255
			4 2768				485.3311
0 143.96 0 140	322 217.0784 <sup>2</sup> 160 180 200 2	27 29.1416 1	280 300	9083 338.3433 9083 338.3433 9083 340	413.26 2 360 380 400	596 453.7891 0 420 440 46	485.8148 538.2667 4
143.96 0 140 Minimum: Maximum:	522 217.0784 160 180 200 2	22 29.1416 20.1416 (200 240 260 5.0	280 300 5.0	9083 338.343 320 340 -1.5 50.0	413.26 2 360 380 400	596 453.7891 0 420 440 46	485.8148 538.2667 40441 - 14141 - 1414 - 1414 - 1414 30 480 500 520 540
143.96 0 140 Minimum: Maximum: Mass	322 217.0784 160 180 200 2 Calc. Mass	229.1416 1.29.1416 1.20 240 260 5.0 mDa	280 300 280 300 PPM	0083 338.3433 320 340 -1.5 50.0 DBE	413.26 2 360 380 400 i-FIT	996 453.7891 0 420 440 46 Formula	485.8148 538.2667 40441 - 14141 - 14141 - 1414 30 480 500 520 540



## <sup>1</sup>H NMR of 5-bromo-*N*,*N*-diisopropyl-1H-indole-1-carboxamide






#### Mass spectrum of 5-bromo-N,N-diisopropyl-1H-indole-1-carboxamide

High resolution mass spectrum of 5-bromo-N,N-diisopropyl-1H-indole-1-carboxamide

Elen	nental Co	mposition	n Report						Page 1
Sing Tole Sele	l <b>e Mass</b> rance = 1 cted filter	Analysis 0.0 PPM s: None	/ DBE: n	nin = -1.5	, max = 60	0.0			
Mono 13 for Eleme C: 0-1	iisotopic Ma rmula(e) eva ents Used: 15 H: 0-10	ss, Even Ele aluated with 7 000 N: 0-2	ctron lons 1 results wit O: 0-1 E	thin limits (a Br: 0-1	ill results (u	p to 1000) fo	or each mass)		
Yeung HR08_	chung Chiu, 3 _1202_3 197 (3	3.662) AM (Top,	.4, Ht,10000.0	,0.00,1.00); Si 323	m (SG, 2x3.00 .0769 32	); Cm (175:224 5.0742	t)		TOF MS ES 2.59e
%-					324 0791	200 0705			
	317.1483	318.3046	320.2409	322.0706	524.0761	326.0785	27.0776 329	.2343 331.2304	332.1636 m/
0	316.0	318.0	320.0	322.0	324.0	326.0	328.0	330.0	332.0
Minin Maxin	: חנוח תנוח :		100.0	10.0	-1.5 60.0				
Mass	Cal	c. Mass	mDa	PPM	DBE	i-FIT	Formula		





<sup>13</sup>C NMR of *N*,*N*-diisopropyl-5-phenyl-1H-indole-1-carboxamide







### High resolution mass spectrum of N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide

Elem	nental	Comp	osition	Repor	t						Page 1
Sing Toler Sele	<b>le Ma</b> rance cted f	ss Ana = 5.0 P ilters: No	<b>lysis</b> PM / one	DBE: r	nin = -1(	)0.0, max =	= 1000.0				
Mono 36 for Eleme C: 0-2 KIN-DE TOF M	nisotopio rmula(e ents Us 22 H: EPT-160 15 ES+	c Mass, E ) evaluate ed: 0-26 N: 42010 Y1 H	ed with 1 0-2 O 15 1 36 (0.6	tron lons results v 0-3 Ni 575) AM (C	s vithin limit: a: 0-1 :en,10, 80.00	s (up to 50 cl	osest results 0,1.00); Sm (SC	6 for each 1 G, 2x3.00); S	mass) b (10,10 343.1	.00 ); Cm (1 792	17:57) 3.52e
-											
	321.	1970									
%-	321.	1970 322.20 32	111 3.2114	329.21	08330.3383	334.2956	8335.1107 340	.2362_341.3	051	344.183	2
%	321. 320.0	322.20 322.5	111 3.2114 325.0	329.210 327.5	08330.3383	334.295 332.5 335	8335.1107 340 0 337.5	.2362_341.3	051	344.183 346 345.0	2 .3325_347.3350 
%- 0- Minim Maxim	321. 320.0 mum: mum:	322.20 322.20 32 322.5	11 3.2114 325.0	329.210 327.5 5.0	08330.3383 330.0 5.0	334.295 332.5 335 -100.0 1000.0	8335.1107 340 0 337.5	.2362_341.3 340.0	051 342.5	344.183 346 345.0	2 .3325_347.3350 
%- 0 Minim Maxim Mass	321. 320.0 mum: mum:	322.20 322.5 Calc. M	111 3.2114 325.0	329.21( 327.5 5.0 mDa	08330.3383 330.0 5.0 PPM	334.295 332.5 335 -100.0 1000.0 DBE	8335.1107 340 .0 337.5 i-FIT	.2362 341.3 340.0 Formu	051 342.5	344.183 346 345.0	2 .3325_347.3350 347.5 m/2



<sup>1</sup>H NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-phenyl-1H-indole-1-carboxamide

<sup>13</sup>C NMR of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide





 $^{31} P \ NMR \ of \ 2-(dicyclohexylphosphino)-N, N-di isopropyl-5-phenyl-1 H-indole-1-carboxamide$ 

High resolution mass spectrum of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5-phenyl-1H-

indole-1-carboxamide

Single M	lass Analysis								
Tolerand	e = 10.0 PPM	/ DBE:	min = -1.	5, max = 6	50.0				
Selected	filters: None								
Monoisoto	pic Mass, Even B	Electron lons	6						
16 formula	(e) evaluated wit	th 1 results v	vithin limits	(all results (	up to 1000) fo	or each ma	ass)		
C: 0-33	Used: H: 0-1000 N: 0-	2 0:0-1	P: 0-1						
Yeung Chun QT ESP HE	g Chiu, C33H45N2P R WLM 2009 0721	0 14 71 (1.325)	AM (Cen,4, 80	.00, Ht,10000.0	0,0.00,1.00); Sm	(SG, 2x3.0	0); Cm (44:8	88) 1	TOF MS
100				517.3355					2.
-									
-									
-									
%-				518.3	384				
%				518.3	384				
%-	95.2333 502.3	3759 507.330	04 514.1	518.3	9.3405 523.2526	531.2858	534.1230	540.1349	543.42
% 04	95.2333 502. 495.0 500.0	3759 507.330 505.0	14 514.1 510.0 51	518.3 519 315 15.0 520.	9.3405 523.2526 0 525.0	531.2858	534.1230	540.1349 540.0	543.42
% 04 Minimum:	95.2333 502.3 495.0 500.0	3759 507.330 505.0	<sup>)4</sup> 514.1 510.0 51	518.3 519 315 15.0 520. -1.5	9.3405 523.2526 0 525.0	531.2858	534.1230 535.0	540.1349 540.0	543.42 545.0



<sup>1</sup>H NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide

<sup>13</sup>C NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide





<sup>31</sup>P NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide

High resolution mass spectrum of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide

lemental Compositi	on Report		Page 1
<b>Single Mass Analysis</b> Tolerance = 5.0 PPM Selected filters: None	/ DBE: min = -	5.0, max = 100.0	
Monoisotopic Mass, Even I 3 formula(e) evaluated wi Elements Used: C: 0-25 H: 0-45 N: 0-4 veung Chiung Chiu, 14102009, N PEPT_111109-YEUNG CHUNG	Electron lons th 1 results within lin O: 0-2 P: 0-1 leOH FA, HS CHIU-29 HS 1 110 (2.04)	nits (all results (up to 100 3) AM (Cen,4, 80.00, Ar,10000	00) for each mass) 1.0,0.00,1.00); Sm (SG, 3x3.00); Sb (10,10.00 ); Cm (74:
100-1			419.2840 3.2964
%-			420.2896
%- 398.1919 <sub>400.2396</sub>	407.2465 409.1637	413.2346 414.2347	420.2896 421.2902 425.1840 429.2265 m/z
%- 0 <u>398.1919</u> 400.2396 400.0	407.2465 409.1633 405.0 410	413.2346 414.2347 .0 415.0	420.2896 421.2902 425.1840 429.2265 m/z 420.0 430.0
%- 0 <u>398.1919400.2396</u> 400.0 Minimum: Maximum:	407.2465 409.1633 405.0 410 100.0 _ 5.0	413.2346.414.2347 .0 415.0 -5.0 100.0	420.2896 421.2902 425.1840 429.2265 m/z 420.0 425.0 430.0
%- 0 398.1919 <sub>400.2396</sub> 400.0 Minimum: Maximum: Mass Calc. Mass	407.2465 409.1637 405.0 410 100.0 5.0 mDa PPN	413.2346,414.2347 0 415.0 -5.0 100.0 1 DBE i-FIT	420.2896 421.2902 425.1840 429.2265 420.0 425.0 430.0 m/z F Formula



<sup>1</sup>H NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide

<sup>13</sup>C NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide





# $^{31} P \text{ NMR of } \textit{N,N-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide}$

 $\label{eq:high-resolution} High \ resolution \ mass \ spectrum \ of \ N, N-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1 H-0.5-methoxy-1 H-0.5-methoxy-1$ 

indole-1-carboxamide

Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -5.0, max = 100.0 Selected filters: None Monoisotopic Mass, Even Electron Ions 35 formula(e) evaluated with 1 results within limits (all results (up to Elements Used:	) ) 1000) for each mass)
Monoisotopic Mass, Even Electron Ions 35 formula(e) evaluated with 1 results within limits (all results (up to Elements Used:	) 1000) for each mass)
C: 0-23 H: 0-45 N: 0-4 O: 0-2 P: 0-1 Yeung Chung Chiu, 14102009, MeOH FA, HS DEPT-111109-YEUNG CHUNG CHIU-28 HS 1 31 (0.583) AM (Cen,4, 80.00, Ar,1	000.0,0.00, 1.00), On (00, 0.00), Ob (10, 10.00), On (1.79
100 %- 330.3411 341.3071 353.2657 <sup>359.3184</sup> 37	392.2559 4.5956 381.2986 407.2462
320.0 330.0 340.0 350.0 360.0 370.0	380.0 390.0 400.0 410.0
Minimum: -5.0 Maximum: 100.0 _5.0 100.0	
Mass Calc. Mass mDa PPM DBE i	-FIT Formula
391.2499 391.2514 -1.5 -3.8 6.5 9	7.7 C22 H36 N2 O2 P



<sup>1</sup>H NMR of *N*,*N*-diisopropyl-5-methoxy-2-(diphenylphosphino)-1H-indole-1-carboxamide

<sup>13</sup>C NMR of *N*,*N*-diisopropyl-5-methoxy-2-(diphenylphosphino)-1H-indole-1-carboxamide





<sup>31</sup>P NMR of *N*,*N*-diisopropyl-5-methoxy-2-(diphenylphosphino)-1H-indole-1-carboxamide

High resolution mass spectrum of *N*,*N*-diisopropyl-5-methoxy-2-(diphenylphosphino)-1H-indole-1-carboxamide



# **Chapter 2: X-Ray structure of ligands**

X-Ray structure of 1-(2-(dicyclohexylphosphino)-5-fluoro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one



# X-Ray data of 1-(2-(dicyclohexylphosphino)-5-fluoro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one

Table 1. Crystal data and structure refinement for BCYCC13 (24 Aug 2009). Identification code ycc13 Empirical formula C27 H40 F N2 O P Formula weight 458.58 Temperature 296(2) K Wavelength 0.71073 Å Crystal system Orthorhombic Space group Pna2(1) Unit cell dimensions a = 20.2705(13) Å b = 11.0357(6) Å c = 11.7327(6) Å Volume 2624.6(3) Å3 Ζ 4 Density (calculated) 1.161 Mg/m<sup>3</sup> Absorption coefficient 0.132 mm<sup>-1</sup> F(000) 992 Crystal size 0.20 x 0.16 x 0.12 mm<sup>3</sup> Theta range for data collection 2.01 to 27.41°. Index ranges Reflections collected 17164 Independent reflections 5155 [R(int) = 0.1006] Completeness to theta = 27.41° 99.8 % Absorption correction Max. and min. transmission 0.9843 and 0.9740 Refinement method Data / restraints / parameters 5155/1/289 Goodness-of-fit on F2 1.001 Final R indices [I>2sigma(I)] R indices (all data) Absolute structure parameter 0.00 Largest diff. peak and hole

α= 90°. β= 90°.  $\gamma = 90^{\circ}$ . -26<=h<=23, -14<=k<=11, -11<=1<=15 Semi-empirical from equivalents Full-matrix least-squares on F<sup>2</sup> R1 = 0.0556, wR2 = 0.0693 R1 = 0.1518, wR2 = 0.0879 0.198 and -0.235 e.Å-3





# X-Ray data of 1-(5-chloro-2-(dicyclohexylphosphino)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one

Table 1. Crystal data and structure refinement for	BCYCC2 (27 May 2009).	
Identification code	ycc2	
Empirical formula	C <sub>27</sub> H <sub>40</sub> N <sub>2</sub> O P Cl	
Formula weight	475.03	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.6643(2) Å	α= 96.526(2)°.
	b = 8.1492(2) Å	β= 92.228(2)°.
	c = 22.0029(5) Å	γ = 95.727(2)°.
Volume	1356.78(6) Å <sup>3</sup>	
Z	2	
Density (calculated)	1.163 Mg/m <sup>3</sup>	
Absorption coefficient	0.220 mm <sup>-1</sup>	
F(000)	512	
Crystal size	0.40 x 0.40 x 0.38 mm <sup>3</sup>	
Theta range for data collection	0.93 to 27.60°.	
Index ranges	-9<=h<=9, -10<=k<=10, -28<	=1<=28
Reflections collected	36558	
Independent reflections	6156 [R(int) = 0.1909]	
Completeness to theta = $27.60^{\circ}$	97.6 %	
Absorption correction	Semi-empirical from equivaler	nts
Max. and min. transmission	1.000 and 0.789	
Refinement method	Full-matrix least-squares on F2	6
Data / restraints / parameters	6156 / 0 / 293	
Goodness-of-fit on F2	1.003	
Final R indices [I>2sigma(I)]	R1 = 0.0548, wR2 = 0.1041	
R indices (all data)	R1 = 0.2922, wR2 = 0.1290	
Largest diff neak and hole	0.210 and 0.171 a \$-3	

1

X-Ray structure of 1-(2-(dicyclohexylphosphino)-5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one



# X-Ray data of 1-(2-(dicyclohexylphosphino)-5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one

# Table 1. Crystal data and structure refinement for BCYCC1 (26 May 2009). Identification code ycc1

Empirical formula Formula weight Temperature Wavelength Crystal system Space group Unit cell dimensions

Volume Z Density (calculated) Absorption coefficient F(000) Crystal size Theta range for data collection Index ranges Reflections collected Independent reflections Completeness to theta = 27.34° Absorption correction Max. and min. transmission Refinement method Data / restraints / parameters Goodness-of-fit on F2 Final R indices [I>2sigma(I)] R indices (all data) Largest diff. peak and hole

C<sub>28</sub> H<sub>40</sub> F<sub>3</sub> N<sub>2</sub> O P 508.59 296(2) K 0.71073 Å Monoclinic P2(1)/n a = 7.6284(2) Åα= 90°. b = 14.7521(3) Å β= 95.343(2)°. c = 25.1897(6) Å  $\gamma = 90^{\circ}$ . 2822.40(12) Å3 4 1.197 Mg/m3 0.139 mm<sup>-1</sup> 1088  $0.40 \ge 0.34 \ge 0.30 \text{ mm}^3$ 1.60 to 27.34°. -9<=h<=9, -18<=k<=18, -32<=l<=32 35867 6350 [R(int) = 0.1029] 99.6 % Semi-empirical from equivalents 1.000 and 0.836 Full-matrix least-squares on F2 6350 / 12 / 349 1.004 R1 = 0.0682, wR2 = 0.1676 R1 = 0.1641, wR2 = 0.2141 0.524 and -0.259 e.Å-3

X-Ray structure of 1-(2-(dicyclohexylphosphino)-5-methoxy-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one



# X-Ray data of 1-(2-(dicyclohexylphosphino)-5-methoxy-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one

Table 1. Crystal data and structure refinement for BCYCC17 (8 Oct 2009). Identification code ycc17 Empirical formula  $C_{28} \, H_{43} \, N_2 \, O_2 \, P$ Formula weight 470.61 Temperature 296(2) K Wavelength 0.71073 Å Crystal system Monoclinic Space group P2(1)/c Unit cell dimensions a = 13.8715(4) Å b = 12.0586(4) Å c = 16.4889(7) Å Volume 2755.81(17) Å<sup>3</sup> Ζ 4 Density (calculated) 1.134 Mg/m<sup>3</sup> Absorption coefficient 0.125 mm<sup>-1</sup> F(000) 1024 Crystal size Theta range for data collection 2.09 to 27.50°. Index ranges Reflections collected 19921 Independent reflections Completeness to theta = 27.50° 99.8 % Absorption correction Nulti-scan Max. and min. transmission 0.9754 and 0.9682 Refinement method Data / restraints / parameters 6320 / 0 / 298 Goodness-of-fit on F<sup>2</sup> 0.993 Final R indices [I>2sigma(I)] R indices (all data) Largest diff. peak and hole 0.199 and -0.190 e.Å-3

α= 90°. β= 92.343(3)°.  $\gamma = 90^{\circ}$ . 0.26 x 0.26 x 0.20 mm<sup>3</sup> -18<=h<=15, -15<=k<=13, -19<=l<=21 6320 [R(int) = 0.1197] Full-matrix least-squares on F2 R1 = 0.0658, wR2 = 0.0788 R1 = 0.2157, wR2 = 0.1035

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X-Ray structure of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide

# X-Ray data of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide

Table 1. Crystal data and structure refinement forBCYCC9 (6 Aug 2009).Identification codeycc9Empirical formulaC33 H45 N2 O PFormula weight516.68Temperature296(2) KWavelength0.71073 ÅCrystal systemMonoclinic

Volume Ζ Density (calculated) Absorption coefficient F(000) Crystal size Theta range for data collection Index ranges Reflections collected Independent reflections Completeness to theta = 27.31° Absorption correction Max. and min. transmission Refinement method Data / restraints / parameters Goodness-of-fit on F2 Final R indices [I>2sigma(I)] R indices (all data) Largest diff. peak and hole

Space group Unit cell dimensions C2/c a = 34.0668(14) Å α= 90°. b = 8.0051(3) Å β= 126.475(2)°. c = 27.0907(11) Å  $\gamma = 90^{\circ}$ . 5940.7(4) Å3 8 1.155 Mg/m3 0.120 mm<sup>-1</sup> 2240 0.20 x 0.14 x 0.08 mm3 1.87 to 27.31°. -33<=h<=43, -9<=k<=10, -34<=l<=28 20511 6633 [R(int) = 0.1242] 98.8 % Semi-empirical from equivalents 0.9905 and 0.9764 Full-matrix least-squares on F2 6633/0/334 0.997 R1 = 0.0725, wR2 = 0.1077 R1 = 0.2202, wR2 = 0.1425 0.224 and -0.226 e.Å-3

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# X-Ray data of N,N-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide

Table 1. Crystal data and structure refinement for BCYCC24 (9 Jul 2010). Identification code ycc24 Empirical formula  $C_{22} \ H_{35} \ N_2 \ O_2 \ P$ Formula weight 390.49 Temperature 296(2) K 0.71073 Å Wavelength Crystal system Orthorhombic P2(1)2(1)2(1) Space group a = 14.1131(8) Å Unit cell dimensions b = 15.0301(7) Å c = 22.7013(13) Å 4815.4(4) Å<sup>3</sup> Volume Ζ 8 1.077 Mg/m3 Density (calculated) Absorption coefficient 0.131 mm<sup>-1</sup> F(000) 1696 Crystal size 1.62 to 27.37°. Theta range for data collection Index ranges Reflections collected 26064 Independent reflections Completeness to theta = 27.37° 99.4 % Absorption correction Muti-scan Max. and min. transmission 0.9844 and 0.9617 Refinement method 10769 / 16 / 484 Data / restraints / parameters Goodness-of-fit on  $\mathrm{F}^2$ 0.900 Final R indices [I>2sigma(I)] R indices (all data) Absolute structure parameter 0.4(5) Largest diff. peak and hole 0.183 and -0.199 e.Å-3

α= 90°. β= 90°.  $\gamma = 90^{\circ}$ . 0.30 x 0.20 x 0.12 mm<sup>3</sup> -13<=h<=18, -19<=k<=16, -15<=l<=29 10769 [R(int) = 0.1434] Full-matrix least-squares on F2 R1 = 0.0831, wR2 = 0.1495 R1 = 0.3126, wR2 = 0.2335

1

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# **Chapter 2: NMR spectrum of cross-coupling products**

<sup>1</sup>H NMR of entry 1







<sup>13</sup>C NMR of entry 2





<sup>13</sup>C NMR of entry 3









<sup>1</sup>H NMR of entry 6















<sup>13</sup>C NMR of entry 10










#### <sup>1</sup>H NMR of entry 14







#### <sup>1</sup>H NMR of entry 15







### **Chapter 3: Supporting data of precursors and ligands**

#### Synthesis of N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1a)



General procedures for condensation reaction:

Benzimidazole (2.36g, 20 mmol) was dissolved in 40ml THF in dropping funnel and added dropwisely to the 60ml THF solution contained 1.2 equiv NaH (60% in mineral oil, 0.96g, 24 mmol) at 0°C. NaH was washed with hexane (20 ml  $\times$  3) under N<sub>2</sub>. The mixture stirred for 1 h at room temperature. After recooling to 0 °C 1.4 equiv N,N-diisopropylcarbamoylchloride (4.58g, 28 mmol) dissolved in 40 ml THF are added to the mixture dropwisely and the mixture is stirred at room temperature over night. Solvent was removed by vacuum. DCM 300 ml and water 100 ml was added to the mixture and the organic phase was separated. The remaining water phase was further extracted with 200 ml DCM twice. The combined organic phase was washed with brine and concentrated. The concentrated mixture was applied to  $3 \times 3$  cm silca pad and eluted with dichloromethane. The organic solvent was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in The white powder of vacuum. N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (4.26g, 87%) was obtained after column chromatography. Melting point: 95.3-96.5°C; <sup>1</sup>H NMR (400 MHz,

CDCl<sub>3</sub>)  $\delta$  1.443 (t, J = 6.8Hz, 12H), 3.78-3.85 (m, 2H), 7.28 (s, 1H), 7.35-7.39 (m, 1H), 7.61-7.83 (m, 1H), 7.84 (d, J = 2.0 Hz, 1H), 8.06 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.9, 49.0, 112.0, 120.3, 123.3, 124.3, 132.5, 140.3, 143.0, 149.4 (Complex unresolved C-P splitting was observed); IR (cm<sup>-1</sup>) 3081.14, 3004.29, 2971.89, 2932.78, 1690.49, 1481.08, 1445.25, 1377.46, 1344.46, 1301.23, 1213.79, 1136.61, 1064.74, 1027.83, 952.93, 890.93, 829.02, 758.54, 609.88; MS (EI): m/z (relative intensity) 245 (M<sup>+</sup>, 42), 145 (11), 128 (74), 118 (58), 86 (100); HRMS: calcd. for C<sub>14</sub>H<sub>19</sub>N<sub>3</sub>OH<sup>+</sup>: 246.1606, found 246.1610.

# <u>Synthesis of 2-(dicyclohexylphosphino)</u> N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (2a)

#### General procedures for ligand synthesis:

N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.23 g, 5.0 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under nitrogen atmosphere. The solution was cooled to -78 °C in dry ice/acetone bath. Titrated n-BuLi (5.5 mmol) was added dropwise by syringe. After the reaction mixture was stirred for an hour at -78°C, chlorodicyclohexylphosphine (1.33 ml, 6.0 mmol) dissolved in 5 ml THF was added dropwise by syringe. The reaction was allowed to warm to room temperature and stirred overnight. Solvent was removed under vacuum. After the solvent was removed under vacuum, the crude product was applied to

column chromatography and the pure product was then dried under vacuum. White solid of title compound (1.61g, 73%) was obtained. Melting point: 205.2-206.8°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.11-2.70 (m, 34H), 3.39-3.60 (m, 2H), 7.29-7.36 (m, 3 H), 7.89-7.91 (m, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.8, 26.2, 27.0, 30.0, 33.0, 34.9, 110.0, 120.0, 122.7, 123.5, 133.9, 143.7, 150.0, 153.0, 153.3 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -15.95; IR (cm<sup>-1</sup>) 2926.88, 2848.80, 1693.42, 1437.21, 1371.58, 1329.53, 1300.93, 1255.22, 1201.02, 1147.90, 1028.78, 1002.16, 829.67, 748.43; MS (EI): *m/z* (relative intensity) 440 (M<sup>+</sup>, 3), 398 (31), 358 (73), 276 (33), 244 (100), 231 (25), 198 (14), 149 (29); HRMS: calcd. for C<sub>26</sub>H<sub>40</sub>N<sub>3</sub>OPH<sup>+</sup>: 442.2987, found 442.3004.

# <u>Synthesis of N,N-diisopropyl</u> <u>2-(diisopropylphosphino)-1H-benzo[d]im</u>idazole-1-carboxamide (2b)



General procedures for the synthesis of ligand 2a were followed. N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.23 g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodiisopropylphosphine (0.95ml, 6.0 mmol) were used to afford N,N-diisopropyl-2-(diisopropylphosphino)-1H-benzo[d]imidazole-1-carboxamide (1.21 g, 67%) as orange solid compound. Melting point: 103.4-104.7°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.12-1.66 (m, 26H), 2.19-2.79 (m, 2H), 3.48-3.53 (m, 2H), 7.29-7.37 (m, 3H), 7.86-7.89 (m, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  19.7, 20.6, 23.1, 25.1, 110.0, 120.0, 122.7, 123.6, 133.8, 133.9, 143.6, 149.5, 153.2, 153.5 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -7.66; IR (cm<sup>-1</sup>) 2967.35, 2869.78, 1696.43, 1456.76, 1434.64, 1373.05, 1330.37, 1304.47, 1258.39, 1206.15, 1151.88, 1032.17, 829.88, 746.24; MS (EI): *m/z* (relative intensity) 361 (M<sup>+</sup>, 2), 318 (2), 276 (37), 244 (18), 233 (18), 191 (24), 149 (17); HRMS: calcd. for C<sub>20</sub>H<sub>32</sub>N<sub>3</sub>OPH<sup>+</sup>: 362.2361, found 362.2365.

# <u>Synthesis of 2-(di-tert-butylphosphino)</u> N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (2c)



General procedures synthesis of ligand followed. for the 2a were N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.23 g, 5.0 mmol), n-BuLi (5.5 mmol), and Di-tertbutylchlorophosphine (1.14 ml, 6.0 mmol) were used to afford 2-(di-tert-butylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.26 g, 65%) as white solid compound. Melting point:  $179.2-181.7^{\circ}$ C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.11-1.71 (m, 30H), 3.63 (m, 2H), 7.28-7.37 (m, 3H), 7.86-7.89 (m, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) δ 20.3, 21.4, 30.3, 30.5, 33.7, 46.7, 51.1, 110.2,

120.3, 122.6, 123.6, 132.9, 133.8, 133.8, 143.9, 149.8, 153.0, 153.5 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  14.35; IR (cm<sup>-1</sup>) 2966.55, 1698.01, 1467.64, 1436.03, 1369.71, 1320.08, 1257.55, 1200.60, 1072.82, 1029.41, 914.88, 827.80, 748.38, 596.73, 546.15; MS (EI): *m/z* (relative intensity) 388 (M<sup>+</sup>, 0), 346 (2), 332 (100), 276 (12), 234 (11), 205 (15), 149 (8); HRMS: calcd. for C<sub>22</sub>H<sub>36</sub>N<sub>3</sub>OPH<sup>+</sup>: 390.2674, found 390.2676.

# <u>Synthesis of N,N-diisopropyl</u> 2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide (2d)



General procedures synthesis of ligand followed. for the 2a were N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.23 g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodiphenylphosphine (1.33 ml, 6.0 mmol) were used to afford N,N-diisopropyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide (1.24g, 58%) as white solid compound. Melting point:  $182.5-184.3^{\circ}$ C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.22-1.46 (m, 12H), 3.48-3.60 (m, 2H), 7.28-7.39 (m, 9H), 7.60-7.87 (m, 4H), 7.872 (d, J = 0.8Hz, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.5, 49.2, 110.1, 120.7, 123.0, 124.1, 128.5, 128.6, 129.3, 133.9, 134.1, 134.2, 144.0, 149.4, 152.7,

152.8 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)
δ -25.44; IR (cm<sup>-1</sup>) 2974.70, 1694.01, 1434.97, 1371.91, 1332.10, 1303.00, 1255.05,
1201.96, 1154.08, 1028.23, 829.83, 747.36, 693.97; MS (EI): *m/z* (relative intensity)
428 (M<sup>+</sup>, 1), 386 (14), 344 (57), 301 (25), 244 (100), 223 (20), 201 (29), 183 (45), 159
(16); HRMS: calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>3</sub>OPH<sup>+</sup>: 430.2048, found 430.2047.

# <u>Synthesis of 2-(diethylphosphino)</u> <u>N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (2e)</u>



General procedures synthesis for the of ligand 2a were followed. N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.23 g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodiethylphosphine (0.73 ml, 6.0 mmol) were used to afford N,N-diisopropyl-2-(diethylphosphino)-1H-benzo[d]imidazole-1-carboxamide (0.86 g, 52%) as white solid compound. Melting point: 89.6-92.5°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.12-1.16 (m, 6H), 1.45 (d, J = 6.4 Hz, 12H), 1.88-1.98 (m, 2H), 2.12-2.19 (m, 2H), 3.52 (t, J = 5.6 Hz, 2H), 7.29-7.34 (m, 3H), 7.86-7.87 (M, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) & 9.8, 10.0, 18.4, 20.1, 20.4, 20.6, 109.8, 119.8, 120.9, 122.8, 123.6, 134.2, 143.6, 149.7, 155.1, 155.3 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>) δ -28.99; IR (cm<sup>-1</sup>) 2964.92, 2931.77, 2873.92, 1692.74, 1458.29, 1430.67, 1372.97, 1329.45, 1303.45, 1261.05, 1205.70, 1154.14, 1029.23, 830.66, 744.74; MS (EI): *m/z* (relative intensity) 332 (M<sup>+</sup>, 3), 304 (45), 290 (38), 262 (15), 248 (100), 228 (23), 207 (22), 177 (28), 149 (28); HRMS: calcd. for C<sub>18</sub>H<sub>28</sub>N<sub>3</sub>OPH<sup>+</sup>: 334.2048, found 334.2043..

Synthesis of 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole (2f)



General procedures synthesis ligand followed. for the of 2a were 1-methyl-1H-benzo[d]imidazole (0.66 g, 5.0 mmol) which is commercially available, n-BuLi (5.5 mmol), and chlorodicyclohexylphosphine (1.33 ml, 6.0 mmol) were used to afford 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole (0.98 g, 60%) as white solid compound. Melting point: 113.2-114.7°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.21-1.39 (m, 10H), 1.76-1.80 (m, 8H), 1.97-1.99 (m, 2H), 2.32-2.39 (m, 2H), 3.98 (d, J = 1.6 Hz, 2H), 7.30-7.41 (m, 3H), 7.87-7.91 (m, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) δ 26.2, 26.6, 26.8, 27.0, 29.2, 29.3, 30.2, 30.3, 31.1, 31.3, 33.4, 33.5, 109.4, 119.8, 121.9, 122.5, 136.3, 144.1, 154.4, 154.6 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -22.55; IR (cm<sup>-1</sup>) 2921.43, 2847.08, 1443.52, 1406.85, 1318.98, 1270.75, 1235.00, 1002.19, 809.49, 758.68,

724.40; MS (EI): *m*/*z* (relative intensity) 328 (M<sup>+</sup>, 8), 245 (100), 213 (2), 164 (25); HRMS: calcd. for C<sub>20</sub>H<sub>29</sub>N<sub>2</sub>PH<sup>+</sup>: 329.2147, found 329.2133.

# Synthesis of 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole (2g)



General procedures followed. for the synthesis of ligand 2a were 1-methyl-1H-benzo[d]imidazole (0.66 g, 5.0 mmol) which is commercially available, n-BuLi (5.5 mmol), and chlorodicyclopentylphosphine (1.29 ml, 6.0 mmol) were used to afford 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole (1.17 g, 65%) as white solid compound. Melting point: 74.5-78.4°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) § 1.26-1.29 (m, 2H), 1.48-1.73 (m, 12H), 2.02-2.06 (m, 2H), 2.63-2.66 (m, 2H), 4.01 (d, J = 1.6 Hz, 3H), 7.29-7.32 (m, 2H), 7.38-7.40 (m, 1H), 7.85-7.87 (m, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) δ 25.5, 26.5, 26.6, 31.1, 37.0, 37.1, 110.0, 120.0, 122.0, 122.6, 136.1, 144.1, 156.8, 157.0 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>) δ -24.34; IR (cm<sup>-1</sup>) 2944.91, 2857.45, 1447.26, 1406.21, 1365.01, 1314.55, 1272.97, 1233.63, 1129.77, 1084.77, 904.08,

807.87, 733.84, 681.80, 541.10, 427.17; MS (EI): *m/z* (relative intensity) 300 (M<sup>+</sup>, 11), 231 (100), 199 (5), 164 (27); HRMS: calcd. for C<sub>18</sub>H<sub>25</sub>N<sub>2</sub>PH<sup>+</sup>: 301.1834, found 301.1826.

#### Synthesis of 5,6-dimethyl-1H-benzo[d]imidazole (1b)



#### General procedures for 1b synthesis:

4,5-Dimethyl-1,2-phenylenediamine (2.72, 0.02 mole) which is commercially available was treated with 1.15 ml formic acid (1.5 equiv, 0.03 mole). The mixture was heated under a water bath at 100°C for two hours. After cooling, sodium hydroxide was added slowly until the mixture was just alkaline to litmus. The crude product was washed with 50ml cold water and 150ml DCM and the organic phase was separated. The remaining water phase was further extracted with 200 ml DCM twice. The combined organic phase was washed with brine and concentrated, following the drying over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuum. The brown powder (2.75g, 94%) was obtained. Melting point: 184.2-188.5°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.3 (s, 1H), 6.44 (s, 1H), 7.35 (s, 2H), 7.89 (1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  18.8, 20.3, 118.6, 127.9, 131.7, 132.2, 139.9 (Complex unresolved C-P splitting was observed); MS (EI): *m/z* (relative intensity) 146 (M<sup>+</sup>, 100), 131 (94), 118 (8), 104 (3), 91 (13), 87 (5), 77 (5); HRMS: calcd. for C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>H<sup>+</sup>: 147.0922, found 147.0927.

#### Synthesis of

# N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1c) General procedures for condensation reaction:

5,6-dimethyl-1H-benzo[d]imidazole, 1b, (2.92g, 20 mmol) was dissolved in 40ml THF in dropping funnel and added dropwisely to the 60ml THF solution contained 1.2 equiv NaH (60% in mineral oil, 0.96g, 24 mmol) at 0°C. NaH was washed with hexane (20 ml  $\times$  3) under N<sub>2</sub>. The mixture stirred for 1 h at room temperature. After recooling to 0 °C 1.4 equiv N,N-diisopropylcarbamoylchloride (4.58g, 28 mmol) dissolved in 40 ml THF are added to the mixture dropwisely and the mixture is stirred at room temperature over night. Solvent was removed by vacuum. DCM 300 ml and water 100 ml was added to the mixture and the organic phase was separated. The remaining water phase was further extracted with 200 ml DCM twice. The combined organic phase was washed with brine and concentrated. The concentrated mixture was applied to  $3 \times 3$  cm silca pad and eluted with dichloromethane. The organic solvent was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuum. The reddish brown powder of N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (4.10g, 75%)

was obtained after column chromatography. Melting point: 117.1-119.5°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.44 (d, *J* = 6.8 Hz, 12H), 2.41 (d, *J* = 2.8 Hz, 6H), 3.79-3.86 (m, 2H), 7.41 (s, 1H), 7.58 (s, 1H), 7.95 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.0, 20.3, 20.8, 48.8, 112.2, 120.1, 130.9, 132.1, 133.5, 139.4, 141.5, 149.7 (Complex unresolved C-P splitting was observed); IR (cm<sup>-1</sup>) 2971.93, 1681.36, 1496.99, 1433.01, 1345.52, 1304.23, 1248.68, 1211.19, 1144.93, 1097.41, 1044.36, 1019.94, 994.95, 909.64, 842.74, 754.86, 646.71, 616.50, 585.00, 554.32, 524.15, 433.79; MS (EI): *m/z* (relative intensity) 273 (M<sup>+</sup>, 42), 173 (11), 145 (26), 128 (61), 86 (100); HRMS: calcd. for C<sub>16</sub>H<sub>23</sub>N<sub>3</sub>OH<sup>+</sup>: 274.1919, found 274.1922.

# <u>Synthesis of 2-(dicyclohexylphosphino)</u> <u>N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (2h)</u>

General procedures for ligand synthesis:

N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1.365g, 5.0 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under nitrogen atmosphere. The solution was cooled to -78 °C in dry ice/acetone bath. Titrated n-BuLi (5.5 mmol) was added dropwise by syringe. After the reaction mixture was stirred for an hour at -78°C, chlorodicyclohexylphosphine (1.33 ml, 6.0 mmol) dissolved in 5 ml THF was added dropwise by syringe. The reaction was allowed to warm to room temperature and stirred overnight. Solvent was removed

under vacuum. After the solvent was removed under vacuum, the crude product was applied to column chromatography and the pure product was then dried under vacuum. White solid of title compound (1.31g, 56%) was obtained. Melting point: 162.5-165.3°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.26-1.95 (m, 34H), 2.39 (d, *J* = 3.6 Hz, 6H), 3.49 (m, 2H), 7.09 (s, 1H), 7.65 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  19.9, 20.2, 20.4, 20.5, 20.6, 46.2, 50.6, 110.4, 120.7, 131.0, 132.2, 133.6, 139.9, 146.8, 149.2, 160.5 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -16.35; IR (cm<sup>-1</sup>) 2970.33, 1697.80, 1634.45, 1515.61, 1438.33, 1373.10, 1331.74, 1298.93, 1234.28, 1208.02, 1157.10, 1035.95, 810.58, 626.04; MS (EI): *m/z* (relative intensity) 468 (M<sup>+</sup>, 9), 426 (27), 386 (64), 343 (9), 304 (18), 272 (100), 259 (23), 177 (55); HRMS: calcd. for C<sub>28</sub>H<sub>44</sub>N<sub>3</sub>OPH<sup>+</sup>: 470.3300, found 470.3292.



N,N-diisopropyl-2-(diisopropylphosphino)-5,6-dimethyl-1H-benzo[d]imidazole-1-car boxamide (1.11g, 57%) as orange solid compound. Melting point: 94.8-96.4°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.07-1.95 (m, 26H), 2.39 (d, *J* = 2.0 Hz, 6H), 3.51 (s, 2H), 7.10 (s, 1H), 7.63 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  19.7, 20.2, 20.4, 20.6, 110.1, 119.8, 131.6, 132.5, 132.9, 142.3, 149.8, 152.0, 152.3 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -8.07; IR (cm<sup>-1</sup>) 2963.39, 2868.49, 1695.01, 1464.11, 1434.71, 1373.01, 1332.31, 1308.69, 1209.16, 1154.84, 1027.41, 1003.84, 878.00, 838.52, 619.02; MS (EI): *m/z* (relative intensity) 389 (M<sup>+</sup>, 2), 346 (100), 304 (46), 273 (15), 262 (18), 219 (28), 177 (28), 86 (18); HRMS: calcd. for C<sub>22</sub>H<sub>36</sub>N<sub>3</sub>OPH<sup>+</sup>: 390.2674, found 390.2660.

# <u>Synthesis of 2-(di-tert-butylphosphino)-N,N-diisopropyl</u> 5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (2j)



General procedures of ligand 2h followed. for the synthesis were N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1.365g)5.0 mmol) which is commercially available, n-BuLi (5.5)mmol), and Di-tertbutylchlorophosphine (1.14 ml, 6.0 mmol) were used to afford 2-(di-tert-butylphosphino)-N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-ca rboxamide (1.00g, 48%) as white solid compound. Melting point:  $168.4-171.6^{\circ}$ C; <sup>1</sup>H

NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.14-1.68 (m, 30H), 2.63 (d, J = 2.8 Hz, 6H), 3.62-3.65 (m, 2H), 7.10 (s, 1H), 7.65 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.2, 20.5, 30.3, 30.5, 33.7, 110.3, 120.2, 131.5, 132.4, 132.9, 142.6, 150.1, 151.9, 152.2 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  13.95; IR (cm<sup>-1</sup>) 2966.65, 1696.82, 1466.79, 1436.62, 1368.95, 1311.06, 1202.72, 1169.01, 1061.29, 1026.91, 910.66, 889.34, 864.47, 837.57, 807.97, 623.78, 591.78, 527.86; MS (EI): *m*/*z* (relative intensity) 416 (M<sup>+</sup>, 0), 374 (3), 360 (100), 318 (5), 304 (10), 262 (15), 233 (28), 177 (20); HRMS: calcd. for C<sub>24</sub>H<sub>40</sub>N<sub>3</sub>OPH<sup>+</sup>: 418.2987, found 418.2992.

# <u>Synthesis of N,N-diisopropyl-5,6-dimethyl-2-(diphenylphosphino)</u> <u>1H-benzo[d]imidazole-1-carboxamide (2k)</u>



General procedures for the synthesis of ligand 2h were followed. N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (0.546g,2.0 commercially mmol) which is available, n-BuLi (2.2)mmol), and chlorodiphenylphosphine (0.53)ml, 2.4 mmol) were used to afford N,N-diisopropyl-5,6-dimethyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carbo xamide (0.38g, 42%) as white solid compound. Melting point:  $174.6-176.8^{\circ}$ C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.28-1.37 (m, 12H), 2.38 (d, J = 5.6 Hz, 6H), 3.4-3.61 (m,

2H), 7.11-7.36 (m, 7H), 7.55-8.33 (m, 5H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.2, 20.5, 110.2, 120.6, 128.4, 128.5, 129.1, 132.0, 132.8, 132.9, 133.5, 133.8, 134.0, 134.5, 142.7, 149.7, 151.4, 151.5 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -25.66; IR (cm<sup>-1</sup>) 3050.16, 2967.16, 2928.78, 1691.23, 1434.42, 1405.18, 1371.81, 1334.72, 1304.95, 1208.83, 1152.97, 1090.58, 1025.99, 883.41, 840.40, 746.11, 692.54, 623.60, 586.65, 507.68, 431.67; MS (EI): *m*/*z* (relative intensity) 456 (M<sup>+</sup>, 1), 414 (15), 372 (45), 346 (9), 329 (27), 272 (100), 256 (22), 201 (25), 183 (49); HRMS: calcd. for C<sub>28</sub>H<sub>32</sub>N<sub>3</sub>OPH<sup>+</sup>: 458.2361, found 458.2369.

# <u>Synthesis of N,N-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino)</u> <u>1H-benzo[d]imidazole-1-carboxamide (21)</u>



General procedures of ligand 2h followed. for the synthesis were N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1.365g)5.0 mmol) which is commercially available, n-BuLi (5.5)mmol), and chlorodi(o-tolyl)phosphine (1.492,6.0 mmol) afford were used to N,N-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino)-1H-benzo[d]imidazole-1-carbo xamide (1.60g, 77%) as white solid compound. Melting point:  $188.2-191.7^{\circ}$ ; <sup>1</sup>H

NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.22-1.46 (m, 12H), 2.38 (d, *J* = 6.8 Hz, 6H), 2.42 (s, 6H), 3.50-3.58 (m, 2H), 7.11-7.31 (m, 9H), 7,61 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$ 20.2, 20.5, 20.6, 21.0, 21.3, 110.2, 120.5, 125.6, 126.3, 128.5, 129.2, 130.0, 131.7, 131.9, 132.0, 133.1, 133.2, 133.3, 133.6, 135.0, 142.2, 142.4, 142.9, 149.6, 150.7, 150.8 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -39.43; IR (cm<sup>-1</sup>) 3051.33, 2966.69, 1690.59, 14444.41, 1372.89, 1327.06, 1204.19, 1155.99, 1058.60, 835.46, 748.82, 714.18, 586.55, 447.71; MS (EI): *m*/*z* (relative intensity) 442 (M<sup>+</sup>, 9), 400 (18), 357 (19), 272 (100), 229 (18), 207 (73), 187 (19), 165 (13); HRMS: calcd. for C<sub>30</sub>H<sub>36</sub>N<sub>3</sub>OPH<sup>+</sup>: 486.2674, found 486.2661..

# <u>Synthesis of 2-(dicyclopentylphosphino)-N,N-diisopropyl-5,6-dimethyl</u> -<u>1H-benzo[d]imidazole-1-carboxamide (2m)</u>



General procedures for the synthesis of ligand 2h were followed. N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide 5.0 (1.365g, mmol) which is commercially available, n-BuLi (5.5)mmol), and chlorodicyclopentylphosphine (1.29 ml, 6.0 mmol) were used to afford 2-(dicyclopentylphosphino)-N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-c arboxamide (1.37g, 62%) as white solid compound. Melting point: 171.4-172.8°C; <sup>1</sup>H

NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.27-2.44 (m, 30H), 2.54 (s, 6H), 3.54 (s, 2H), 7.10 (s, 1H), 7.61 (s, 1H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  20.2, 20.4, 25.5, 26.3, 30.5, 30.7, 110.1, 119.7, 131.6, 132.2, 132.8, 142.3, 149.7, 154.0, 154.2 (Complex unresolved C-P splitting was observed); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>)  $\delta$  -19.70; IR (cm<sup>-1</sup>) 2952.49, 2864.67, 1696.68, 1436.25, 1372.36, 1331.78, 1305.86, 1211.37, 1157.86, 1060.90, 1027.97, 1003.17, 894.49, 842.03, 625.66, 586.69, 523.09; MS (EI): *m/z* (relative intensity) 440 (M<sup>+</sup>, 3), 398 (32), 358 (75), 331 (8), 315 (10), 276 (34), 259 (7), 244 (100), 228 (27); HRMS: calcd. for C<sub>26</sub>H<sub>40</sub>N<sub>3</sub>OPH<sup>+</sup>: 442.2987, found 442.2970.

# Chapter 3: NMR spectrum and mass spectrum of precursors and ligands

<sup>1</sup>H NMR of *N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide



<sup>13</sup>C NMR of *N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide





#### Mass spectrum of N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

High resolution mass spectrum of N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

Elem	nenta	I Composit	ion Report								Page 1
Sing Toler Seler	rance	ass Analysi = 10.0 PPN filters: None	<b>s</b> 1 / DBE:n	nin = -1.	5, max :	= 60.0					
Monoi 112 fo Eleme C: 0-1 Yeung HR08_	isotopi ormula ents Us 14 H: Chung 1218_1	c Mass, Even (e) evaluated v sed: 0-1000 N: 0 Chiu, C14N3OH1s 3 (0.063) AM (Cel	Electron lons vith 1 results w -3 O: 0-19 ) n,4, 80.00, Ht,100	ithin limits 00.0,0.00,1.	(all resul	ts (up to	1000) fo	or each m	ass)		TOF MS ES+
100					8 8 S	246.	1610				1.22e3
%											
0 2	29.1428	230.2485 233.	2424 238.1341.23	39.0910	245	.0798	247.1	630 48.1669 250	0.1702	256.2626	257.2500
	230	0.0 232.5	235.0 237.5	240.0	242.5	245.0	247.5	250.0	252.5	255.0	257.5 m/z
4inim Maxim	um: um:		100.0	10.0	-1.5 60.0						
lass		Calc. Mass	mDa	PPM	DBE	i-F	IT	Formula	1		
246.10	610	246.1606	0.4	1.6	6.5	0.2		C14 H2	0 112	0	



<sup>1</sup>H NMR of 2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

 $^{13}C\ NMR\ of\ 2-(dicyclohexylphosphino)-N, N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide$ 





# <sup>31</sup>P NMR of 2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

#### High resolution mass spectrum of

# 2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

	Compositio	n Report				Page 1
Single Ma Tolerance Selected f	ass Analysis = 5.0 PPM / filters: None	DBE: m	nin = -5	.0, max = 1	00.0	
Monoisotopi 474 formula Elements U: C: 0-30 H:	c Mass, Even Ele (e) evaluated wit sed: 0-42 N: 0-5	ectron lons n 1 results O: 0-5 P:	within lim 0-1 96	its (all results Ru: 0-1	; (up to 10	000) for each mass)
EUNG CHUNG KIN-DEPT-180	3 cHIU, C26H40N3C 220010-C26H40N3C	P P-HS 1 55 (1	.043) AM (	Cen,4, 80.00, Ar	,5000.0,0.00 442.3	0,1.00); Sm (SG, 2x3.00); Sb (10,10.00 ); Cm (30:63) 3004 2.29e4
%						
%- 366.242	1381.2979394	.7491 409.16	667 414.27	19 425.1696	437.1940	443.3068 444.3117 464.2839 480.2759
% 0 <u>366.242</u> <u>370</u>	<sup>1</sup> 381.2979 394 380 390	.7491 409.16 400	367 414.27 410	19 425.1696 420 430	437.1940	443.3068 444.3117 464.2839 480.2759 m/z 450 460 470 480
%- 0 366.242 370 Sinimum: laximum:	1 <u>381.2979 394</u> 380 390	.7491 409.16 400 100.0	367 414.27 410 5.0	19 425.1696 420 430 -5.0 100.0	437.1940 440	443.3068 444.3117 464.2839 480.2759 450 460 470 480 m/z
%- 0 366.242 0 370 finimum: faximum: fass	1 381.2979 394 380 390 Calc. Mass	.7491 409.16 400 100.0 mDa	667 414.27 410 5.0 PPM	19 425.1696 420 430 -5.0 100.0 DBE	437.1940 440 i-FIT	443.3068 444.3117 464.2839 480.2759 450 460 470 480 Formula



<sup>1</sup>H NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-1H-benzo[d]imidazole-1-carboxamide

<sup>13</sup>C NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-1H-benzo[d]imidazole-1-carboxamide





# <sup>31</sup>P NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-1H-benzo[d]imidazole-1-carboxamide

#### High resolution mass spectrum of

#### N,N-diisopropyl-2-(diisopropylphosphino)-1 H-benzo[d] imidazole-1-carboxamide

								i age i
Single Mass Analysis	S							
Tolerance = 10.0 PPN	1 / DBE: m	nin = -1.5	, max	= 60.0				
Selected filters: None			,					
Monoisotopic Mass, Even	Electron lons		2					
Flements Lised	th 1 results with	hin limits (a	all result	s (up to 10	00) for each	mass)		
C: 0-26 H: 0-1000 N. 0	-3 0.0-1 P	0-1						
Yeung Chung Chiu, C20N3OPH3	32	. 0-1						
QT_ESP_HR_WLM_2009_0617	_3 39 (0.741) AM (	Cen,4, 80.00	, Ht,1000	0.0,0.00,1.00)	; Sm (SG, 2x3.0	00); Cm (37:	61)	TOF MS ES+
100			362.23	65				2.03e3
1								
~								
70								
				363.2407				
339.3418.341.3101	348,4087 353	.2727 359	3215	364.2423	370.1537	381 208	9	390.2707
0 339.3418.341.3101 335.0 340.0 3	348.4087 353	355.0	360.0	364.2423	370.1537	381.298	395.0	390.2707 m/z
0 339.3418.341.3101 335.0 340.0 3	348.4087 353 345.0 350.0	.2727 359 355.0	.3215 360.0	364.2423 365.0 37	370.1537 0.0 375.0	381.298 380.0	3 385.0	390.2707 390.0 m/z
0 339.3418.341.3101 335.0 340.0 3 Iinimum:	348.4087 353 345.0 350.0	355.0	.3215 360.0 -1.5	364.2423 365.0 37	370.1537 0.0 375.0	381.298 380.0	385.0	390.2707 390.0 m/z
0 339.3418.341.3101 335.0 340.0 3 inimum: laximum:	348.4087 353 345.0 350.0 100.0	.2727 359 355.0 10.0	.3215 360.0 -1.5 60.0	364.2423 365.0 37	370.1537 0.0 375.0	381.298 380.0	3 385.0	390.2707 390.0 m/z
0 339.3418.341.3101 335.0 340.0 3 finimum: faximum: lass Calc. Mass	348.4087 353 345.0 350.0 100.0 mDa	2727 359 355.0 10.0 PPM	0.3215 360.0 -1.5 60.0 DBE	364.2423 365.0 37	370.1537 0.0 375.0	381.298 380.0	385.0	390.2707 m/z 390.0
0 339.3418.341.3101 335.0 340.0 3 inimum: aximum: MSS Calc. Mass	348.4087 353 345.0 350.0 100.0 mDa	2727 359 355.0 10.0 PPM	0.3215 360.0 -1.5 60.0 DBE	364.2423 365.0 37 i-FI1	370.1537 0.0 375.0 Form	381.298 380.0 ula	3 385.0	390.2707 390.0 m/z



<sup>1</sup>H NMR of 2-(di-tert-butylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

<sup>13</sup>C NMR of 2-(di-tert-butylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide





# <sup>31</sup>P NMR of 2-(di-tert-butylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

#### High resolution mass spectrum of

# 2-(di-tert-butylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

Liementa	ai com	positio	n Report							Page	1
Single M Tolerance Selected	ass Ar e = 10. filters:	n <b>alysis</b> 0 PPM None	/ DBE:	min = -1	.5, max = 6	0.0					
Ionoisotop 8 formula( Ilements U 2: 0-26 H feung Chung XT_ESP_HR	oic Mass e) evalu Ised: I: 0-1000 Chiu, C22 WLM_20	, Even Ele ated with ) N: 0-3 2N3OPH36 09_0617_2 (	ectron lons 1 results w O: 0-1 56 (1.061) AM	vithin limits P: 0-1 A (Cen,4, 80, 39	(all results (u 00, Ht,10000.0,0 0.2676	p to 1000	)) for eac	h mass) 3.00); Cm (4	13:69)	TOF MS E 4.1	S+ 5e3
% 0 366.223	5 369.23	60 379.17	<sup>717</sup> 381.2994	387.1775	391.2712 392.2733	397.2804	406.2695	409.1636	415.2186	419.2775	-
365.0	370.0	375.0	380.0	385.0 3	90.0 395.0	400.0	405.0	410.0	415.0	420.0	n/z
linimum: Maximum:			100.0	10.0	-1.5 60.0						
ass	Calc.	Mass	mDa	PPM	DBE	i-FIT	For	rmula			
00 0000	390 2	674	0.0	0.5							



<sup>1</sup>H NMR of *N*,*N*-diisopropyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide

<sup>13</sup>C NMR of *N*,*N*-diisopropyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide





# $^{31} P \text{ NMR of } \textit{N,N-diisopropyl-2-(diphenylphosphino)-1} H-benzo[d] imidazole-1-carboxamide$

#### High resolution mass spectrum of

#### N,N-diisopropyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide

Elem	ental Compositi	on Report					Page 1
Singl Tolera Selec	e Mass Analysis ance = 10.0 PPM ted filters: None	/ DBE: I	nin = -1.	5, max =	60.0		
Monois 20 form Elemer C: 0-26 Yeung C QT_ESF 100 -	sotopic Mass, Even E nula(e) evaluated wit nts Used: 5 H: 0-1000 N: 0- Chung Chiu, C26N3POH2 9-HR_WLM_2009_0617_	Electron lons h 1 results wi 3 O: 0-1 F 8 1 67 (1.268) AM	thin limits 2: 0-1 (Cen,4, 80.0	(all results 00, Ht,10000. 430.2	(up to 1000) 0,0.00,1.00); Sn 047	for each mass) n (SG, 2x3.00); Cm (36:76	i) TOF MS ES+ 4,32e3
%					431.2084		
0	404.1295 409.1654	415.2227419.2	778 425.	1404	432.2119	437.1963443.2682	452.1874 455.1548
	405.0 410.0	415.0 42	20.0 42	5.0 430.	0 435.0	440.0 445.0	450.0 455.0
Minimu Maximu	im: im:	100.0	10.0	-1.5 60.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula	
430.20	47 430.2048	-0.1	-0.2	14.5	0.6	C26 H29 N3	O P



<sup>1</sup>H NMR of 2-(diethylphosphino)-*N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

<sup>13</sup>C NMR of 2-(diethylphosphino)-*N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide





# <sup>31</sup>P NMR of 2-(diethylphosphino)-*N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

#### High resolution mass spectrum of

# $\label{eq:linear} 2-(diethylphosphino)-\textit{N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide}$

Liemeni	al Compos	ition Report							Page 1
Single N Foleranc Selected	lass Analys e = 5.0 PPN filters: None	e <b>is</b> 1 / DBE: m	in = -5.0,	max = 1(	0.0				
Aonoisoto 70 formul Elements U 2: 0-19 H EUNG CHUI (IN-DEPT-1)	pic Mass, Even a(e) evaluated Jsed: H: 0-42 N: 0- NG cHIU, C18H28 30220010-C18H28	n Electron lons with 1 results v 5 O: 0-5 P: ( 3N3OP BN3PO-HS 1 117 (2	vithin limits ( )-1 2.207) AM (Cer	all results 1,4, 80.00, Ar 334.2043	(up to 1000	)) for each 1.00); Sm (S <sup>o</sup>	mass) 3, 2x3.00); S	b (10,10.00 );	Cm (38:162) 5.36e4
%-				335.	2076				
%- 309.07	86 318.2994	320.2486 323.226	<sup>33</sup> 329.1914	335.:	2076 16.2114 340.2	138 35	0.2037 352.1	850 356.1874	4 360.3231,
% 309.07 310.0	86 318.2994 315.0	320.2486 323.226 320.0 325.0	<sup>33</sup> 329.1914 330.0	335.1 33 335.0	2076 6.2114 340.2 340.0	2138 35	0.2037 352.1 350.0	850 356.1874 355.0	4 360.3231 m/z 360.0
%- 0309.07 310.0 Minimum: Maximum:	86 318.2994, 315.0	320.2486 323.226 320.0 325.0 100.0	<sup>33</sup> 329.1914 330.0 5.0	335.3 335.0 -5.0 100.0	2076 6.2114 340.2 340.0	2138 35 345.0	0.2037 352.1 350.0	850 356.1874 355.0	4 360.3231 m/z 360.0
%	86 318.2994. 315.0 Calc. Mass	320.2486 323.226 320.0 325.0 100.0 5 mDa	<sup>33</sup> 329.1914 330.0 5.0 PPM	335. 33 335.0 -5.0 100.0 DBE	2076 6.2114 340.2 340.0 i-FIT	138 35 345.0 Formu	0.2037 <sub>352.1</sub> 350.0	850 356.1874 355.0	4 360.3231 m/z 360.0





 $^{13}{\rm C}\ {\rm NMR}\ {\rm of}\ 2\mbox{-}({\rm dicyclohexylphosphino})\mbox{-}1\mbox{-}{\rm methyl-}1{\rm H}\mbox{-}{\rm benzo}[d]{\rm imidazole}$ 







High resolution mass spectrum of 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole

Eleme	ntal Com	npositio	on Report						Page 1
Single Tolerar Selecte	Mass An nce = 10. ed filters:	n <b>alysis</b> 0 PPM None	/ DBE: r	nin = -5	.0, max = 1	00.0			
Monoiso 36 formu Element C: 0-25 Yeung Ch	itopic Mass Jla(e) evalu Is Used: H: 0-45 Jung Chiu, 141	, Even E lated with N: 0-4	lectron lons h 1 results wit P: 0-1 eOH FA, HS	thin limits	(all results (u	ip to 1000	) for each	mass)	
100	TU9-YEUNG	CHUNG C	HIU-24 HS 1 67	(1.251) AN	I (Cen,4, 80.00,	Ar,5000.0,0.	00,1.00); Sm 329.	(SG, 2x3.00) 2133	; Sb (10,10.00 ); Cm (54:91 2.98e4
%									
0 23	30.2464	253.920	)6 274.	2733 285.2	301.1405	313.2809	327.1987	330.2180 331.2212	345.2103 354.2705
230	240	250	260 270	280	290 300	310	320 3	330 340	350 360 m/z
Minimum Maximum	1:		100.0	10.0	-5.0 100.0				
lass	Calc.	Mass	mDa	PPM	DBE	i-FIT	Form	ula	



#### <sup>1</sup>H NMR of 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole

<sup>13</sup>C NMR of 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole





# <sup>31</sup>P NMR of 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole

High resolution mass spectrum of 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole

Elementa	al Composit	ion Report				Page 1
Single M Tolerance Selected	ass Analysi e = 5.0 PPM filters: None	s / DBE: m	in = -5.0	, max = 100	0.0	
Monoisotop 225 formula Elements L C: 0-19 H yEUNG cHUN	ic Mass, Even a(e) evaluated sed: : 0-42 N: 0-5 IG cHIU, C18H25I	Electron lons with 1 results w O: 0-5 P: 0	vithin limits )-1	all results (i	up to 100	0) for each mass)
100	0220010-C18H25	N2P-HS 1 22 (0.42	1) AM (Cen,	4, 80.00, Ar,500	0.0,0.00,1.0 301.18	00); Sm (SG, 2x3.00); Sb (10,10.00 ); Cm (10:41) 2.43e4
%-					302.	.19
0 1	64.45 187.03.2	03.03 217.06 2	0.25 261	13 274.27 282.2	8 304	4.26 317.18 352.25 366.23 397.19 409.17 m/z
140	160 180	200 220	240	260 280	300	320 340 360 380 400
Minimum: Maximum:		100.0	5.0	-5.0 100.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula



<sup>1</sup>H NMR of *N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide

<sup>13</sup>C NMR of *N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide




### Mass spectrum of N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide

High resolution mass spectrum of N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide

Elemental Com	position R	leport					Page 1
Single Mass Ar Tolerance = 50. Selected filters:	a <b>lysis</b> ) PPM / None	DBE: min :	= -1.5, max	= 60.0			
Monoisotopic Mass 9 formula(e) evalua Elements Used: C: 0-16 H: 0-1000 Yeung Chung Chiu, C16 QT ESP HR WLM 20	Even Electro ted with 1 res N: 0-3 O N3OH23 09_0720_1 56 (1	on lons cults within lin : 0-1 1.061) AM (Cen,	nits (all results 4, 80.00, Ht,1000	(up to 1000) for 0.0,0.00,1.00); Sm (5	each mass) SG, 2x3.00); Cm	(51:81)	TOF MS ES+
100			274.1922				1.99e3
0 250.9917 256 250.0 255.0	2657 261.1343 260.0	267.2678	274.1922	949 282,2810 284	.2971291.0725	297.6112	304.2624
100 % 0 250.9917 256 250.0 255.0 binimum: laximum:	2657 261.1343 0 260.0 1	267.2678 265.0 27 00.0 50	274.1922 275.1 0.0 275.0 .0 -1.5 60.0	949 282,2810 284 280.0 285.0	.2971291.0725 290.0	297.6112 295.0 300.0	1.99e3 304.2624 
100 % 0 250.9917 256 250.0 255.0 tinimum: laximum: lass Calc.	2657 261.1343 ) 260.0 1 Mass m	267.2678 265.0 27 00.0 50 Da PPI	274.1922 275.1 0.0 275.0 .0 -1.5 60.0 M DBE	949 282.2810_284 280.0_285.0 i-FIT	.2971291.0725 290.0 Formula	297.6112 295.0 300.0	1.99e3 304.2624 0 305.0

<sup>1</sup>H NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-

benzo[d]imidazole-1-carboxamide



<sup>13</sup>C NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-



<sup>31</sup>P NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-

benzo[d]imidazole-1-carboxamide



High resolution mass spectrum of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



<sup>1</sup>H NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5,6-dimethyl-1H-



<sup>13</sup>C NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5,6-dimethyl-1H-

benzo[d]imidazole-1-carboxamide



## <sup>31</sup>P NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5,6-dimethyl-1H-

benzo[d]imidazole-1-carboxamide



High resolution mass spectrum of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide

lementa	I Com	positio	1 Report						Page 1
Single Ma Tolerance Selected f	ass An = 10.0 filters: 1	<b>alysis</b> ) PPM None	/ DBE: I	min = -5.	0, max =	100.0			
Aonoisotop 0 formula( Elements U 0: 0-25 H Yeung Chung 0EPT-111109	ic Mass, e) evalua sed: : 0-45 Chiu, 141 -YEUNG (	Even Ele ated with N: 0-4 ( 02009, MeC CHUNG CH	ctron lons 1 results wi 0: 0-2 P: 0 0H Fa, HS 1U-31-HS 1 1	thin limits 0-1	(all results	(up to 1000)	) for each mass	5)	5 /10 10 00 \· Cm /84·1
100							390.1	2660	4.71e4
%-								391.2712	
-									
0 230.24	78 26	33.1671 27	4.2732	305.2137	313.2797 3	141.3040 <sup>353</sup>	.2664 381.2976	392.2757	425.1824 m/7
0 230.24 220	78 26 240	53.1671 27 260	4.2732 280	305.2137 300	313.2797 3 320	341.3040 <sup>353</sup> 340 36	.2664 381.2976 30 380	392.2757 400	425.1824 m/z 420
0 230.24 220 tinimum: taximum:	78 20 240	260 260	280 100.0	305.2137 300 10.0	313.2797 3 320 -5.0 100.0	341.3040 353 340 36	.2664 381.2976 50 380	392.2757 400	425.1824 m/z 420
Ainimum: Maximum: Mass	78 28 240 Calc.	53.1671 27 260 Mass	4.2732 280 100.0 mDa	305.2137 300 10.0 PPM	313.2797 3 320 -5.0 100.0 DBE	341.3040 353 340 36 i-FIT	.2664 381.2976 50 380 Formula	392.2757 400	425.1824 420 m/z

## <sup>1</sup>H NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-



<sup>13</sup>C NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-

benzo[d]imidazole-1-carboxamide



## <sup>31</sup>P NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-

## benzo[d]imidazole-1-carboxamide



High resolution mass spectrum of 2-(di-tert-butylphosphino)-N,N-diisopropyl-5,6-dimethyl-1H-

Element	al Composition	1 Report				Page 1
Single M Toleranc Selected	lass Analysis e = 5.0 PPM / filters: None	DBE: m	in = -5.0,	max = 10	0.0	
Ionoisoto; 4 formula 2 lements L 2: 0-25 H 2eung Chung 2EPT-11110	bic Mass, Even Ele (e) evaluated with Jsed: 1: 0-45 N: 0-4 C g Chiu, 141002009, Me 9-YEUNG CHUNG CHI	ctron lons 1 results wi D: 0-2 P: OH FA, Is U-30 HS 1 24	thin limits (a 0-1 4 (0.453) AM (i	all results (u Cen,4, 80.00, A 41	p to 1000) Ar,10000.0,0.1 8.2992	for each mass) 00,1.00); Sm (SG, 2x3.00); Sb (10,10.00 ); Cm (2:51 3.64e4
% 391	.2523 397.1876 400	.1854	409.1644	415.2236	419.303	6 <sup>054</sup> 425.1817 434.2959 437.1947
390.0	395.0 400.0	405.0	410.0	415.0	420.0	425.0 430.0 435.0 440.0
Minimum: Maximum:		100.0	5.0	-5.0 100.0		
ass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
18 2002	418 2987	0 5	1 2	6 5	27 2	004 Mile 110 0 0

<sup>1</sup>H NMR of *N*,*N*-diisopropyl-5,6-dimethyl-2-(diphenylphosphino)-1H-

benzo[d]imidazole-1-carboxamide



<sup>13</sup>C NMR of *N*,*N*-diisopropyl-5,6-dimethyl-2-(diphenylphosphino)-1H-



<sup>31</sup>P NMR of *N*,*N*-diisopropyl-5,6-dimethyl-2-(diphenylphosphino)-1H-

benzo[d]imidazole-1-carboxamide



High resolution mass spectrum of *N*,*N*-diisopropyl-5,6-dimethyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide

lementa	I Composition	n Report				Page 1
olerance	ss Analysis	DBE: m	in = -5.0	max = 1(	0.0	
selected f	ilters: None					
Ionoisotopi	c Mass, Even Ele	ctron lons				
80 formula	(e) evaluated with	1 results w	ithin limits	all results	(up to 1000) (	for each mass)
Cements Us C: 0-30 H:	ed: 0-42 N: 0-5 C	0.0-5 P.0	)-1			
EUNG CHUNG	G cHIU, C28H32N3PC	) )	/~1			
IN-DEPT-180	220010-C28H32N3P	D-HS 1 66 (1.)	249) AM (Ce	n,4, 80.00, Ar,5	5000.0,0.00,1.00	)); Sm (SG, 2x3.00); Sb (10,10.00 ); Cm (36:131)
.00						1.0265
%-						150.01
						459.24
331 14	250 07 260 02	0000000				460.24
0	353.27 300.23 373	.19 381.30	397.19 409.	16 425.18	437.19 457.	21 481.14 489.23 511.21 m/z
340	350 360 370	380 390	400 41	0 420 43	0 440 450	460 470 480 490 500 510
inimum:				-5.0		
3 37 3 POLLIPS +		100.0	5.0	100.0		
orvenuenti:						
ass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula

## <sup>1</sup>H NMR of *N*,*N*-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino)-1H-



<sup>13</sup>C NMR of *N*,*N*-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino)-1H-

benzo[d]imidazole-1-carboxamide



## <sup>31</sup>P NMR of N,N-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino)-1H-

### benzo[d]imidazole-1-carboxamide



High resolution mass spectrum of *N*,*N*-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino)-1H-benzo[d]imidazole-1-carboxamide



<sup>1</sup>H NMR of 2-(dicyclopentylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-



<sup>13</sup>C NMR of 2-(dicyclopentylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-

benzo[d]imidazole-1-carboxamide



## <sup>31</sup>P NMR of 2-(dicyclopentylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-

benzo[d]imidazole-1-carboxamide



High resolution mass spectrum of 2-(dicyclopentylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide

Elementa	I Com	positi	on Report						Page 1
Single Ma Folerance Selected f	ass Ar = 20. filters:	n <b>alysis</b> 0 PPM None	/ DBE:	min = -5.(	), max = 1	100.0			
Ionoisotopi 0 formula(e lements Us : 0-27 H: eung Chung IN-DEPT-250	ic Mass e) evalu sed: 0-42 Chiu 022010 C	, Even E ated witi N: 0-5 16N3OPH	ilectron lons n 1 results w O: 0-1 P: 40 HS 2 298 (5	ithin limits ( 0-1 607) AM (Cen	all results (1	up to 1000) fo	each mass)	0): Sb (10 1	0.00 )· Cm (288-298)
00								442	.2970 4.23e3
155.	5018	217.	1078 253.5	962 282.274	6 304.262	<sup>6</sup> 351.9887	374.5496	425.1834	443.3013 444.3028
160	180	200	220 240	260 280	300 320	340 360	380 400	420 44	40 460
inimum: aximum:			100.0	20.0	-5.0 100.0				
lass	Calc.	Mass	mDa	PPM	DBE	i-FIT	Formula		
42.2970	442.2	987	-1.7	-3.8	8.5	1.2	C26 H41	N3 0	P

# **Chapter 3: X-Ray structure of ligands**

X-Ray structure of 2-(dicyclohexylphosphino)-N,N-diisopropyl-1Hbenzo[d]imidazole-1-carboxamide



## X-Ray data of 2-(dicyclohexylphosphino)-N,N-diisopropyl-1Hbenzo[d]imidazole-1-carboxamide

Table 1. Crystal data and structure refinement for BCYCC26 (13 May 2010). Identification code ycc26 Empirical formula C26 H40 N3 O P Formula weight 441.58 Temperature 296(2) K Wavelength 0.71073 Å Monoclinic Crystal system Space group P2(1)/n Unit cell dimensions a = 8.1446(2) Å α= 90°. b = 15.3354(3) Å β= 93.3020(10)°. c = 20.6322(4) Å  $\gamma = 90^{\circ}$ . Volume 2572.70(9) Å3 Ζ 4 Density (calculated) 1.140 Mg/m3 0.128 mm<sup>-1</sup> Absorption coefficient F(000) 960 Crystal size 0.32 x 0.30 x 0.28 mm<sup>3</sup> 1.66 to 27.35°. Theta range for data collection Index ranges -10<=h<=10, -19<=k<=19, -25<=l<=26 Reflections collected 31334 Independent reflections 5790 [R(int) = 0.0654] Completeness to theta = 27.35° 99.3 % Absorption correction Semi-empirical from equivalents Max. and min. transmission 0.9650 and 0.9601 Refinement method Full-matrix least-squares on F2 Data / restraints / parameters 5790 / 12 / 316 Goodness-of-fit on F2 1.004 Final R indices [I>2sigma(I)] R1 = 0.0643, wR2 = 0.1751 R indices (all data) R1 = 0.1221, wR2 = 0.2092 Largest diff. peak and hole 0.177 and -0.576 e.Å-3

1

X-Ray structure of N,N-diisopropyl 2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide



# X-Ray data of N,N-diisopropyl 2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide

Identification and	BCYCC32 (14 Jul 20)	0).
Empirical formula	ycc32	
Empirical formula	C <sub>26</sub> H28 N <sub>3</sub> O P	
Formula weight	429.48	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.6184(2) Å	α= 9
	b = 15.6177(4) Å	β= 90
	c = 20.1914(7) Å	$\gamma = 90$
Volume	2402.41(12) Å <sup>3</sup>	32
Z	4	
Density (calculated)	1.187 Mg/m <sup>3</sup>	
Absorption coefficient	0.136 mm <sup>-1</sup>	
F(000)	912	
Crystal size	0.28 x 0.20 x 0.18 mm <sup>3</sup>	
Theta range for data collection	2.02 to 27.35°.	
Index ranges	-9<=h<=9, -20<=k<=17	-26<=1<=17
Reflections collected	17124	201111
Independent reflections	5369 [R(int) = 0.0626]	
Completeness to theta = $27.35^{\circ}$	99.9 %	
Absorption correction	Semi-empirical from equi	valents
Max. and min. transmission	0.9759 and 0.9629	valents
Refinement method	Full-matrix least-squares	on F <sup>2</sup>
Data / restraints / parameters	5369 / 0 / 280	0111
Goodness-of-fit on F2	1.001	
Final R indices [I>2sigma(I)]	$R_1 = 0.0560 \text{ w}R_2 = 0.110$	12
R indices (all data)	R1 = 0.1162  wR2 = 0.120	13
Absolute structure parameter	-0.13(13)	5
Largest diff neak and hole	0.522	

α= 90°. β= 90°.  $\gamma=90^{\circ}.$ 

1



X-Ray structure of 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole

# X-Ray data of 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole

Table 1. Crystal data and structure refinement for	BCYCC33 (26 Jul 2010).	
Identification code	ycc33	
Empirical formula	C <sub>20</sub> H <sub>29</sub> N <sub>2</sub> P	
Formula weight	328.42	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 10.5931(3) Å	α= 90°.
	b = 10.3544(3) Å	β= 90°.
	c = 34.0185(11) Å	y = 90°.
Volume	3731.33(19) Å <sup>3</sup>	
Z	8	
Density (calculated)	1.169 Mg/m <sup>3</sup>	
Absorption coefficient	0.150 mm <sup>-1</sup>	
F(000)	1424	
Crystal size	0.38 x 0.38 x 0.38 mm <sup>3</sup>	
Theta range for data collection	2.26 to 27.36°.	
Index ranges	-13<=h<=11, -12<=k<=13, -43<	= <=26
Reflections collected	23907	
Independent reflections	4205 [R(int) = 0.0959]	
Completeness to theta = $27.36^{\circ}$	99.4 %	
Absorption correction	Semi-empirical from equivalent	s
Max. and min. transmission	0.9454 and 0.9454	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	4205 / 0 / 208	
Goodness-of-fit on F <sup>2</sup>	1.004	
Final R indices [I>2sigma(I)]	R1 = 0.0629, wR2 = 0.1537	
R indices (all data)	R1 = 0.1468, wR2 = 0.1870	

Largest diff. peak and hole

197

0.328 and -0.236 e.Å-3

1

X-Ray structure of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



# X-Ray data of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide

Table 1. Crystal data and structure refinement for	r BCYCC22 (31 Mar 2010).			
Identification code	ycc22			
Empirical formula	C <sub>28</sub> H <sub>32</sub> N <sub>3</sub> O P			
Formula weight	457.54			
Temperature	296(2) K			
Wavelength	0.71073 Å			
Crystal system	Monoclinic			
Space group	P2(1)			
Unit cell dimensions	a = 7.81540(10) Å	α= 90°.		
	b = 12.6075(2) Å	β= 97.3000(10)°.		
	c = 13.0798(2) Å	$\gamma = 90^{\circ}$ .		
Volume	1278.34(3) Å <sup>3</sup>			
Z	2			
Density (calculated)	1.189 Mg/m <sup>3</sup>			
Absorption coefficient	0.132 mm <sup>-1</sup>			
F(000)	488			
Crystal size	0.50 x 0.50 x 0.48 mm <sup>3</sup>			
Theta range for data collection	2.25 to 27.45°.			
Index ranges	-10<=h<=10, -16<=k<=16, -1	16<=1<=16		
Reflections collected	13582			
Independent reflections	5451 [R(int) = 0.0340]			
Completeness to theta = $27.45^{\circ}$	98.8 %			
Absorption correction	Semi-empirical from equivale	ents		
Max. and min. transmission	1.000 and 0.743			
Refinement method	Full-matrix least-squares on F2			
Data / restraints / parameters	5451 / 1 / 298			
Goodness-of-fit on F <sup>2</sup>	1.002			
Final R indices [I>2sigma(I)]	R1 = 0.0414, wR2 = 0.0949			
R indices (all data)	R1 = 0.0590, wR2 = 0.1041			
Absolute structure parameter	-0.12(8)			
Largest diff. peak and hole	0.176 and -0.191 e.Å-3			

1

X-Ray structure of 2-(dicyclopentylphosphino)-N,N-diisopropyl-5,6-dimethyl -1H-benzo[d]imidazole-1-carboxamide



## X-Ray data of 2-(dicyclopentylphosphino)-N,N-diisopropyl-5,6-dimethyl -1H-benzo[d]imidazole-1-carboxamide

#### Table 1. Crystal data and structure refinement for BCYCC29 (7 Jul 2010). ycc29 Identification code Empirical formula C26 H40 N3 O P 441.58 Formula weight 296(2) K Temperature Wavelength 0.71073 Å Triclinic Crystal system Space group P-1

Volume Z Density (calculated) Absorption coefficient F(000) Crystal size Theta range for data collection Index ranges Reflections collected Independent reflections Completeness to theta =  $27.65^{\circ}$ Absorption correction Max. and min. transmission Refinement method Data / restraints / parameters Goodness-of-fit on F<sup>2</sup> Final R indices [I>2sigma(I)] R indices (all data) Largest diff. peak and hole

Unit cell dimensions

a = 9.3784(2) Å α= 95.0800(10)°. β= 92.0230(10)°. b = 10.9102(2) Å  $\gamma = 113.6220(10)^{\circ}$ . c = 13.9297(3) Å 1296.82(5) Å3 2 1.131 Mg/m3 0.127 mm<sup>-1</sup> 480 0.36 x 0.30 x 0.26 mm<sup>3</sup> 2.05 to 27.65°. -12<=h<=12, -14<=k<=14, -18<=l<=18 23378 5951 [R(int) = 0.0480] 98.4 % Semi-empirical from equivalents 1.000 and 0.785 Full-matrix least-squares on F2 5951/0/280 1.006 R1 = 0.0575, wR2 = 0.1704 R1 = 0.0941, wR2 = 0.1990 0.305 and -0.270 e.Å-3





## X-Ray data of N,N-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino) 1H-benzo[d]imidazole-1-carboxamide

Table 1. Crystal data and structure refinement for BCYCC31 (13 Jul 2010). Identification code ycc31 Empirical formula C30 H36 N3 O P 485.59 Formula weight Temperature 296(2) K Wavelength 0.71073 Å Crystal system Monoclinic P2(1)/c Space group Unit cell dimensions a = 7.5998(13) Å

Volume Z

Density (calculated) Absorption coefficient F(000) Crystal size Theta range for data collection Index ranges Reflections collected Independent reflections Completeness to theta = 27.09° Absorption correction Max. and min. transmission Refinement method Data / restraints / parameters Goodness-of-fit on F2 Final R indices [I>2sigma(I)] R indices (all data) Largest diff. peak and hole

α= 90°. b = 18.648(3) Å β= 93.172(8)°. c = 19.143(3) Å  $\gamma = 90^{\circ}$ . 2708.9(8) Å3 4 1.191 Mg/m<sup>3</sup> 0.128 mm<sup>-1</sup> 1040 0.26 x 0.10 x 0.06 mm<sup>3</sup> 1.53 to 27.09°. -9<=h<=9, -23<=k<=23, -22<=l<=24 35476 5947 [R(int) = 0.6713] 99.5 % Semi-empirical from equivalents 0.9923 and 0.9674 Full-matrix least-squares on F<sup>2</sup> 5947/0/316 0.929 R1 = 0.0841, wR2 = 0.0977 R1 = 0.3264, wR2 = 0.1248 0.237 and -0.311 e.Å-3

203

# **Chapter 3: NMR spectrum of cross-coupling products**

<sup>1</sup>H NMR of entry 1 and 2



<sup>&</sup>lt;sup>13</sup>C NMR of entry 1 and 2









<sup>13</sup>C NMR of entry 4











<sup>13</sup>C NMR of entry 6











<sup>13</sup>C NMR of entry 8





<sup>13</sup>C NMR of entry 9





<sup>13</sup>C NMR of entry 10











<sup>13</sup>C NMR of entry 12




<sup>13</sup>C NMR of entry 13





## <sup>13</sup>C NMR of entry 14











# <sup>13</sup>C NMR of entry 16

